Health and Welfare Canada
Santé et Bien-être social Canada

Status of Diabetes in Canada

Report of Symposium held at Le Chateau, Montebello,
Montebello, Quebec,
May 21, 22, 23, 1985

A project of the Association du Diabète du Québec, the Canadian Diabetes Association and the Juvenile Diabetes Foundation Canada in collaboration with Health and Welfare Canada.

Canada

NATIONAL DIABETES TASK FORCE
COMMISSION NATIONALE D'ÉTUDE SUR LE DIABÈTE

CANADIAN
DIABETES
ASSOCIATION

ASSOCIATION
DU DIABÈTE
DU QUÉBEC

JUVENILE
DIABETES
FOUNDATION

STATUS OF DIABETES

IN CANADA

Report of Symposium held
at Le Chateau, Montebello,
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89-04864/

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I. INTRODUCTION

This document is the result of a tremendous effort made by a number of Canadian scientists, clinicians, and health professionals involved in the field of diabetes. Their effort was coordinated by the National Diabetes Task Force to evaluate "the current status of diabetes in Canada".

The work done by those experts was presented and discussed at a symposium held at Montebello, Quebec on May 21, 22, 23, 1985. Five specific themes were addressed: epidemiology, complications, treatment, education and research in diabetes. From those discussions, a number of conclusions and general recommendations were made; these will serve as a working document for the National Diabetes Task Force. Those recommendations and the working manuscripts are compiled in this document. For easy reference, we have choosen to incorporate at the beginning of the book a list of all the general recommendations. These are then followed by chapters on each of the specific themes; each of these chapters starts by stating the problems followed by the recommendations and then by the working manuscripts. The last chapter summarizes the experience of the Americans with the National Commission on Diabetes held in the 1970s.

The National Diabetes Task force is a joint project of the Association du Diabete du Quebec (Quebec Diabetes Association) (ADQ), the Canadian Diabetes Association (CDA) and the Juvenile Diabetes Foundation (JDF) in collaboration with Health and Welfare Canada. Its broad mandate is to evaluate the status of health care delivery to diabetics across Canada and to make recommendations for improvement.

The Task Force originated from an initiative of the Professional Health Workers Section (PHW) of the CDA who wanted to standardize diabetes education through the development of a model of practice for health professionals. This preliminary project was submitted to Health and Welfare Canada who showed an interest in the project and stimulated discussion on the subject. A first meeting between representatives from the ADQ, CDA and Health and Welfare Canada was held on July 18, 1984. From those discussions, it became obvious that many questions had to be answered before we could standardize diabetes education. Since the answer to many of those questions was not readily available, the creation of a National Diabetes Task Force was suggested. For that purpose, a planning committee was formed representing the ADQ and the CDA. They met in Montreal on September 23, 1984 with Dr. Jo Hauser from Health and Welfare Canada and officially created the National Diabetes Task Force. More recently, the JDF has joined ranks with the other two organizations.

To establish the priorities of the Task Force it was decided to organize this symposium to evaluate the current status of diabetes in Canada. Approximately fifty experts in the field of diabetes from across Canada were invited to participate at this symposium. We are grateful to Oscar Crofford who agreed to share with us his exceptional experience as chairman of the National Commission on Diabetes in the United States held in 1970's. The report of that commission was delivered to the American Congress in December 1975.

The first theme addressed was the **epidemiology** of diabetes in Canada. Before we can approach the problem of health care delivery to diabetics across the country, it is essential that we know exactly the population that we are dealing with. Until now, we have been extrapolating from the report of the USA National Commission on Diabetes. But we know that because of the multiple variables (regional differences, ethnic groups, age of population, etc.), such extrapolations are subject to significant errors. Even the rare epidemiological studies done suggest that there are regional differences in the incidence of diabetes in Canada. It is therefore impossible from the U.S. data, to appreciate the overall incidence of diabetes in Canada and particularly those regional differences across the country; these are some of the questions raised during the symposium as well as the morbidity, the mortality and the socio-economic impact of the disease on the Canadian community.

The second theme discussed was the chronic **complications** of diabetes. If the discovery of insulin by Banting and Best virtually solved the acute problems related to diabetes, it also brought to our attention a series of chronic complications involving the eyes, the kidneys, the peripheral nerves and the cardiovascular system. Those complications have a major socio-economic impact on our community. We know, for example, that diabetes is now the first cause of blindness. We also know that photocoagulation by laser therapy has been shown to be efficient in delaying the progression of diabetic retinopathy. An important question is: do all Canadian diabetics have access to such a treatment? If not, why? What can be done about it? Similar questions are also be raised concerning the other complications.

There is now evidence suggesting that with the appropriate **treatment,** that is with the normalization of blood glucose, we should be able to delay or prevent the appearance and progression of those complications. Over the last couple of years, new technological developments have completely changed our approach to the treatment of diabetes. The use of reflectance meters by patients to measure blood glucose, makes it possible for them to readjust the treatment to normalize their blood glucose. New devices to deliver insulin have made it possible for the diabetics to administer insulin in a more physiologic way, and also made it easier for them to accept intensive insulin therapy. Again a question was raised as to the accessibility of this new technology to the Canadian diabetics.

It has become more and more evident over the last decade that **education** is an important and essential part of the treatment of diabetes. But education of such a heterogenous population (due to differences in age, culture, education, type of diabetes, etc.) becomes very complex and difficult. What makes it even more difficult is the fact that it is not enough to improve their knowledge about the disease; we also have to change their behaviour. Here, we get to the same questions raised by the PHWS of the CDA back in early 1984: what is the ideal system for diabetes education? How does that compare to what we have across Canada? Who has access to such an education system? How are the teachers (PHWS and physicians) trained for such an important task? And just as important, how do we assess the impact of education on the outcome of diabetes?

And finally, the continued improvement of health care delivery to diabetics in Canada depends on **research** in diabetes. It is important to realize that we cannot depend entirely on our neighbours from the South. We, as Canadian scientists, have to participate actively in the research and development in diabetes; otherwise, we will always be one step behind. So the questions we have to address are: what is our participation in diabetes research? How many Canadian investigators do we have? How are they funded? How do we prepare our young investigators? Those are some of the important questions raised.

The answer to those and many other questions are essential if we want to do long term planning to try to solve the problem of diabetes in Canada. It is obvious that we will raise more questions than we will answer. For that reason this symposium should not be considered as the final product of the National Diabetes Task Force; it is only the beginning. This exercise provided us with a list of recommendations. These recommendations will serve as a working document for the National Diabetes Task Force to define the priorities. Study groups will then be organized to work on those priorities and come out with final recommendations during the next year. It will be the responsibility of the Task Force to see that those recommendations be followed and implemented. When this is done, it will be essential that the Task Force becomes a permanent committee: A National Diabetes Advisory Board. This Board would be responsible to stimulate, supervise, evaluate and coordinate the continuing progress in diabetes in Canada.

Jean-Louis Chiasson, M.D.
Chairman,

RECOMMENDATIONS

II. RECOMMENDATIONS FOR FUTURE NATIONAL DIABETES TASK FORCE STUDY GROUPS

EPIDEMIOLOGY OF DIABETES IN CANADA

The recommendations are divided into two main groups: national statistics related to diabetes and local studies on diabetes with special emphasis on research problems.

A. National Statistics

1. Periodic Surveys

Prevalence and incidence data should be obtained through national and regional population-based surveys.

A similar technique used in the United States, the National Health and Nutrition Examination Survey (HANES) has been used to determine prevalence of diabetes in the population. HANES periodically utilizes a probability sample of the U.S. population obtaining data from medical questionnaires, but also, including oral glucose tolerance tests.

2. Provincial Health Care Records

Diabetes should be identified through linkage of records related to physician visits, diabetes supplies including drugs, and hospital discharges. Both primary and secondary diagnoses of diabetes should be utilized.

3. Follow-Up of Survey Repondents

Further information concerning incidence, complications and survival rates should be determined by linking survey cohorts to health and death records.

4. Death Certificate Data

Information based on underlying and contributing causes of death where diabetes is mentioned should be compiled.

By using centralized health records and linkage, extensive data collection can be carried out.

Advantages

This methodology will provide the best estimates of prevalence, mortality and to a lesser extent incidence, free from selection biases inherent in clinical surveys.

Disadvantages

(a) There is a lack of uniformity in routinely available health records.
(b) Population-based surveys are costly.

B. Local Studies

1. New Registries

New registries can provide important information concerning (a) incidence, (b) costs, (c) case-control studies for etiological factors, (d) cohort studies for complications and morbidity.

The diagnosis of diabetes should be standardized using either the National Diabetes Data Group or WHO recommendations.

There is a unique opportunity for provincial governments to play a major role in diabetes registries. The Prince Edward Island Registry serves as an example where the provision of services and/or supplies through a provincial health care plans has been utilized to collect information. Coordination and standardization between provinces would be essential for these registries to be successful and provide the information that is important for health care planning.

2. Investigator-Initiated Etiologic Studies

Cohort and case-control studies should be conducted in multiple local areas. Studies that should be considered include: examination of ethnic origins (e.g. country of birth, North American Indians), review of seasonal incidence rate differences, viral illnesses, HLA typing, socio-economic background, urban versus rural environment, occupation, diet, and physical activity.

3. Examination of Differences Between type 1 and type 2 Diabetes

The risk of complications for both types of diabetes and the relation to economic factors, childhood antecedents, obesity, family history and previous history of gestational diabetes should be established.

4. Mortality Rates and Causes of Death

A comparison of rates and causes of death in type 1 and type 2 diabetes is in need of urgent review.

5. Review of Risk Factors for Vascular Complications

The specific roles of hyperglycemia, hypertension, hyperlipidemia, diet, exercise, obesity, smoking and other risk factors, need to be evaluated in careful epidemiological studies.

6. Assessment of Diabetes Management

A review of natural history of diabetes and assessment of existing intervention strategies that will allow new programs to be developed for treatment of diabetes and its complications.

COMPLICATIONS OF DIABETES IN CANADA

Recommendations are given for specific complications

A. Retinopathy

1. Patients should be educated about the need for eye evaluation and treatment.
2. All type 2 diabetics should have an eye examination (by an Ophthalmologist) at diagnosis.
3. All type 1 diabetics should have an eye examination by an Ophthalmologist within 5 years of diagnosis.
4. All diabetics should be reexamined by an Ophthalmologist annually.
5. Education should be organized for general ophthalmologists, internists, endocrinologists, etc. on the importance of early referral and treatment of diabetic retinopathy.
6. Dissemination of new information (e.g. symposia) to all health professionals should be organized.
7. More retinal specialists interested in diabetes care should be recruited.
8. Research should be stimulated in:
   a) basic science relating to the pathophysiology of diabetes eye disease.
   b) clinical research to evaluate newer treatment modalities.
9. Interested ophthalmologists should be identified and regional centres for treatment should be established.
10. Screening programs for diabetics who do not have access to ophthalmologist services should be developed. (e.g. possibly transporting nurse practitioners, trained in eye examination, to outlying areas).

B. Nephropathy

1. Close attention should be directed to the management of hypertension in all diabetics.

2. Research studies to evaluate the usefulness of microalbuminuria as a marker of early progressive diabetic nephropathy should be initiated and the possible reversibility of this marker with glucose control should be documented in Canada.

3. Once advanced diabetic nephropathy develops (ie. urine protein greater than 300 mg/day, and/or a rise in serum creatinine) the nephrologist should begin to follow the patient along with the endocrinologist or internist. Optimal management of advanced disease should include:
   (a) effective blood pressure control
   (b) early dialysis and transplantation

4. The divisions of nephrology across Canada should take a more active role in establishing multidisciplinary clinical settings (including an endocrinologist, nephrologist, ophthalmologist, nurse clinican, dietitian, social worker, etc.) for the ongoing treatment and clinical investigation of patients with diabetic nephropathy.

5. Canadian scientists should be encouraged to investigate the pathophysiologic mechanisms of diabetic glomerulosclerosis.

C. Neuropathy

1. Every diabetic should have a neurological examination as part of an annual review with the primary care physician.

2. Patient education concerning the existence of diabetic neuropathy with a simple outline of symptoms and signs should be presented in a pamphlet.

3. Quantitative methods of assessment should be developed (eg. computerized electrophysiological tests, quantitative sensory threshold determinations, autonomic function tests) to give objective measures which might be followed to assess responses to therapy more accurately.

4. Further research into the pathophysiology (metabolic disturbances, ischemia) is necessary to allow the development of rationale modes of therapy.

5. Different modes of therapy must be tested rigorously. These include modalities such as: prevention of complications by improved diabetes control and the use of drugs (eg. aldose reductase inhibitors), for metabolic intervention.

D. Macrovascular Disease

1. Accurate, specific and sensitive non-invasive methods to assess macrovascular disease should be developed. This is not only important to diagnose the disease, but is essential for any epidemiologic study and assessment of impact of preventive and treatment resources.

2. New advances in lipoprotein classification and apolipoprotein assays should be recognized to examine a) their impact on atherosclerosis and b) the impact of diabetes on lipoproteins.

3. The metabolism of lipoproteins in diabetics should be explored in order to a) determine what metabolic factors result in increased lipoprotein risk effects; b) anticipate intervention strategies to reverse these risk effects; and c) develop methods to "control" diabetes that also address the other atherogenic factors.

4. The relationship of hyperinsulinemia to atherogenesis should be explored further.

   - Does exogenous insulin administration result in hyperinsulinemia that poses an atherogenic risk?
   - Do the route, timing and type of insulin have an impact on the development of atherosclerosis?

5. The changes in platelet function that are a consequence of diabetes (and not associated atherosclerosis) should be examined. It should also be determined which of these may be influenced by diabetes control and develop strategies to diminish any platelet associated risk.

6. Aggressive and effective antihypertensive therapy in diabetic subjects should be developed and implemented.

7. Aggressive anti-smoking strategies should be developed and implemented.

8. In addition to anti-atherogenic strategies in general, effective foot care measures that will prevent injury to diabetics, particularly to ischemic limbs, should be implemented.

E. General Recommendations

1. Guidelines for the prevention, detection and management of diabetes related long term complications should be developed.

2. The need for regionalization of treatment facitilies in order to implement efficiently the recommended services for both rural and urban diabetic populations should be assessed.

3. The manpower requirements to achieve an acceptable standard of diabetes treatment should be assessed.

4. We should standardize patient and professional information on prevention and treatment of complications.

TREATMENT OF DIABETES MELLITUS IN CANADA

A. Current Therapy of Diabetes Mellitus

The recommendations are:

1. to establish an agreed set of guidelines for health care delivery to diabetes mellitus. It is suggested that this should be addressed by an appropriate working group identified by the Task Force in collaboration with the Canadian Diabetes Association and the Quebec Diabetes Association;

2. to undertake an assessment of the facilities and services presently available for the treatment of diabetes across the country.

3. to identify the shortcomings of those facilities and services and to satisfy the needs as determined.

B. Development of Improved and Innovative Therapies in Diabetes

1. Appropriate model systems for development and assessment of the efficacy of improved therapy in diabetes should be established. A number of possible models were discussed. These range from institutional diabetes research centres, through collaborative organizations with appropriate administrative support and funding. It is suggested that a committee of the Task Force address this problem. The workshop discussed the nature of funding for such research. It was agreed in general that the peer review mechanism is the best established method for determining the merit and priority of proposals in this area. However, it is also suggested that the funding mechanism for this type of work needs to be separated from the established competitions for more basic research related to diabetes. Work in the area of development of improved therapies might be regarded as a category of research and development within the health care system so that existing and possibly new funding arrangements developed through the provincial and federal ministries of health might be explored.

2. As a second recommendation in this area the workshop recognized the importance of training a suitable cadre of health professionals. These professionals would include physicians developing special expertise in the optimal and innovative therapies in diabetes and might be trained within the model systems discussed above. They

would compete for personal support through a process separate from that currently established for research trainees seeking experience designed to qualify them as independent investigators.

C. Diet in the Management of Diabetes Mellitus

1. It is recommended that the curricula for medical and dietitic students be improved to provide adequate training in the dietary management of diabetes.

2. It is also recommended that certification programs for health care professionals specializing in dietary management of diabetes be established. The programs should include requirements for internships, and might be related to systems for continuing education.

3. In order that there be an adequate supply of dietitians, there should be (a) adequate provincial government funding of dietetic internships in teaching hospitals and (b) hospital budgets that encourage preventive care, e.g. outpatient counselling, diabetes education.

   To secure accessibility to diet counselling in the community outside hospitals, the fees of qualified dietitians should be covered directly or indirectly by provincial health care plans.

D. The Use of Oral Hypoglycemic Agents in the Treatment of Diabetes Mellitus

It is recommended that up-to-date information regarding therapy with oral hypoglycemia agents be included in the proposed guidelines for the management of diabetes mellitus.

E. The Use of Available Preparations of Insulin in the Treatment of Diabetes Mellitus

1. The development of an appropriate generic terminology is recommended. This should be undertaken with good liaison between health professionals, manufacturers, and the appropriate regulatory agencies.

2. Further liaison should be developed between the health professionals and the manufacturers in order to provide for continued assessment of the availability and need for particular preparations.

3. The workshop concluded also that there remain good reasons for support in principle of the maintenance of an onshore capacity for production of a full range of insulins.

F. Management of Diabetes in Pregnancy

1. A standardized screening test for gestational diabetes mellitus must be established.

2. It is recommended that consumable materials and apparatus necessary for optimal therapy of diabetes in pregnancy should be provided without charge to this group of persons with diabetes.

3. It is recommended that a registry for diabetes in pregnancy should be established. The objective of this registry in the context of the therapy of diabetes is to provide a means for quality control.

4. The assessment of outcome in a systematic way must be undertaken, for the above reasons.

5. It is important to emphasize that preconception management of diabetes must be appropriate and generalized.

G. Management of Diabetes in Children

1. It is important to obtain information regarding the current level of delivery of health care to children with diabetes across the country.

2. It is recommended that specific guidelines and standards for the management of diabetes in children be established and disseminated.

3. It is also recommended that specific goals for professional education in regard to management of diabetes in children be set.

4. It is imperative to establish that funding-reimbursement mechanisms do not impede delivery of the necessary services.

H. General Recommendations

The following recommendations were adopted by the workshop and accorded high importance and priority.

1. It is necessary to prepare an up-to-date set of guidelines for the professional management of diabetes, as indicated above.

2. It is urgently necessary to undertake a review of the available manpower and facilities in relation to the needs as related to the standards defined, and to determine the shortfall in funding and the sources of monies necessary for solutions to this problem.

3. It is important to determine and establish a system or systems for the development and assessment of improved and innovative modes of treatment in diabetes mellitus.

4. There are compelling reasons for provision of consumable materials and apparatus to identifiable groups of persons with diabetes, including children, pregnant women and the elderly. It is also important to consider the need for, and possible means of, extending this assistance to persons with diabetes in general.

5. There is a need to establish registries for diabetes. Initially these should be set up for diabetes in pregnancy, and for persons with newly diagnosed type 1 diabetes. The objective in the treatment context of these registries would be (a) to provide for assessment of outcomes, quality control, and appropriate corrective responses, and (b) to assist in identification of families and persons at relatively high risk for development of diabetes. This information is also necessary for assessment of risk benefit ratios in this important area of health care.

EDUCATION ON DIABETES MELLITUS IN CANADA

A. Program for Adults with Diabetes

1. Education should be accepted as an integral part of treatment.

2. Education must be multi-disciplinary.

3. Education should be publicly funded.

4. Education should be available to all Canadians with diabetes and their families.

5. Education should be given by properly qualified personnel.

6. Available standards and guidelines should be implemented.

7. There should be a review of existing education facilities across Canada.

B. Program for Children with Diabetes

1. All children should be cared for, or should receive regular review, by a specialized team in a tertiary care facility.

2. The family must be involved in the learning process.

3. The goals of teaching must be directed to an understanding of the patho-physiology of diabetes by the patient and parents and a major goal must be the establishment of new life habits in areas such as eating and exercise.

4. All programs should receive on-going evaluation.

5. Education must be an ongoing process throughout the whole period that the child is under pediatric care.

6. An improved method for transfer of patients from pediatric to adult care must be developed across the country.

C. Nutrition Education for People with Diabetes

1. Nutrition education and counselling are essential in the management of diabetes.

2. Health care systems should provide adequate funding for nutrition education and counselling.

3. There should be an evaluation of the Good Health Eating Guide system.

4. Nutrition education should be part of any health care facility.

D. Education Assessment

1. Psychological factors should be recognized as influencing the management of diabetes with respect to both education and adherence to a treatment program.

2. The Health Belief Model in each individual should be recognized as influencing learning and management.

3. Simulated tests and information from an informant should be used in preference to direct questioning for qualitative assessment of learning by the person with diabetes.

E. Program for Allied Health Professionals

1. A national agency should be established to coordinate a training program for diabetes educators.
2. A long term strategic plan should be developed to assess the objectives and needs for revision of such a program.

3. Cooperation should be encouraged with other licensing agencies and health care agencies to assist in the implementation and evaluation of the program.

4. A national resource base should be established for collecting data, including that on educational tools available.

5. The necessity of the education of the primary care nurse in all active treatment hospitals should be recognized.

F. Program for Physicians

1. A standard curriculum for diabetes education should be developed and made available to associate deans of undergraduate education or their equivalents for use in Canadian medical schools if desired.

2. Information should be obtained on the diabetes content of residency training in Family Medicine, Internal Medicine and Pediatrics.

3. The need for evaluation of the various forms of continuing medical education should be acknowledged.

G. Role of Diabetes Associations, Governments and Industry

1. The responsibilities and priorities which are to be shared among industry, governments, and the voluntary organizations should be identified. A national meeting of the voluntary organizations and industry may be needed to sort out priorities and responsibilities in this area.

2. Provincial governments should recognize the value of diabetes education centres as important tools in the effective management of diabetes mellitus and diabetes education centres should be withdrawn from global budgets and given protected line budgeting for a period of time in order to ensure their proper establishment and development.

H. General Recommendations

1. Model training and treatment facilities should be established to provide state-of-the-art care and education to diabetic patients, and to act as regional teaching sites for training health care professionals.

2. Education research should be funded to identify behaviourally and clinically effective models of professionals and patient education. This should be based on a team of investigators with expertise in clinical diabetes, educational psychology, nursing, dietetics and biostatistics.

3. A Canadian Diabetes Advisory Board should be established to oversee and coordinate diabetes research and educational initiatives. Members should represent researchers, educators, persons with diabetes, volunteer health organizations and professional associations.

4. It is recommended that a national conference on diabetes education be convened with representatives from universities and diabetes education centres and including experts in the area of education, psychology, and other disciplines in order to improve the level of diabetes education in Canada. This conference should be

responsible for establishing methods of evaluation of diabetes education and identify the cost-effectiveness of diabetes education programs in Canada. It is recommended that this conference be jointly sponsored by govenments and the diabetes organizations.

RESEARCH IN DIABETES MELLITUS IN CANADA

1. A sub-committee of the National Diabetes Mellitus Task Force should be established to analyze the implications and the means of implementing the following recommendations.

2. Training grants supported with new funds obtained from government sources should be made available to suitable programs which can recruit potential trainees in a more assured manner.

3. Diabetes Canada should direct a substantial portion of the funds raised to the support of scholarships awards like the Medical Research Council scholarship awards.

4. The issue of coordinating funding between the Medical Research Council and national volunteer organizations should be addressed.

5. The National Diabetes Task Force should support the recommendations of the MRC-RCPSC joint Task Force on Clinician Scientists.

6. The Royal College of Physicians and Surgeons should reduce the amount of clinical training deemed necessary for specialties certification so as to permit trainees to pursue research endeavours in various areas, including diabetes mellitus.

7. The base salary of established clinician scientists should be sufficient to allow them to maximize their research time.

8. Diabetes research and training centres of excellence should be encouraged to develop in Canada. These centres should share relatively uniform guidelines with regards to objectives so that quality assurance of their programs can be done. Extra-mural endowment funding together with governmental (federal and/or provincial) may be a feasible approach in setting up these potential centres.

9. Psycho-social aspects of diabetes management should be included among the various areas of diabetes research topics.

10. A closer collaboration in diabetes research between industries and universities as well as institutions involved in research should be promoted.

EPIDEMIOLOGY

EPIDEMIOLOGY: SUMMARY AND RECOMMENDATIONS

Summary

There is general agreement that epidemiologic data on diabetes in Canada are extremely scarce. Most of the data is poorly obtained and has been inferred from United States data. Health care records both federally and provincially are inadequate yet essential information could be obtained by a small improvement in record keeping. The success of the Prince Edward Island epidemiological study where the provincial government allows registration of patients receiving specific health benefits for diabetes, serves as a model for other provinces in Canada. Improved recording of death certificate data and hospital discharge diagnosis could prove invaluable.

Individual researchers should be encouraged to carry out cohort and case-control studies on specific issues related to both in type 1 and type 2 diabetes.

There is an urgent need for surveys to assess prevalence and costs of diabetes in Canada and to provide health care estimates of the potential costs and medical concerns related to diabetes. The increasing use of record linkage in many of the provinces, would suggest that Canada is in a unique position to obtain information that has previously been unknown to virtually all countries dealing with the health care problems of diabetes.

Canada must consider further major health surveys such as the Canada Health Survey that was abandoned in 1979. A model to review would be the National Health and Nutrition Examination Survey (HANES) which determines the prevalence of diabetes in the United States population. HANES reviews a probability sample of the U.S. population and obtains data from standardized questionnaires. Included in the study are oral glucose tolerance tests, which in the U.S. population, have revealed that the prevalence of diabetes is nearly double that estimated by the questionnaire.

It is recognized that the economic figures provided in these papers, are a gross underestimation of the total cost of diabetes to the health care system. The recommendations provided from the Task Force stress the importance of gathering epidemiological data on diabetes in Canada and should help evaluate the costs and social impact of diabetes.

The epidemiologic analysis of a chronic disease such as diabetes mellitus can provide essential information as to the number of existing cases (prevalence), the number of new cases (incidence), the nature of underlying risk factors and the economic and psycho-social impact on the community. The population studies of cancer and heart disease are examples of programs that have shed new light on the etiology of these diseases and led to ongoing research into the associated environmental and genetic factors.

Only limited information on diabetes is available in Canada. Much of our statistical data are derived from extrapolating population figures and dollar values from the United States. The small number of epidemiological studies performed in Canada have provided some insight into the enormity of the problem. Yet each of these studies has utilized quite different case ascertainment methods and diabetes diagnostic criteria, making comparisons difficult. Similar problems exist in the few studies performed in other countries.

Canada is in the unique position of having a government funded health system that is continuously collecting information through its provincial health care programs and federal agencies such as Statistics Canada, but there are many difficulties in utilizing these data. The information is frequently collected in a non-uniform manner and is largely incomplete. The following recommendations would see the development of national and local projects that would further define problems related to diabetes in Canada and assist in the planning of new research and management programs.

A committee should be established from the National Diabetes Task Force, to work with Health & Welfare Canada and Canadian diabetes organizations, to develop coordinated strategies for further epidemiological studies of diabetes in Canada. The questions and procedures relating to epidemiological research in diabetes could then be formulated with the assistance of the advisory committee.

Recommendations

The recommendations can be divided into two main groups: (1) National statistics related to diabetes and (2) Local studies on diabetes with special emphasis on research problems.

A. National Statistics

1. Periodic Surveys

Prevalence and incidence data should be obtained through national and regional population-based surveys.

A similar technique used in the United States, the National Health and Nutrition Examination Survey (HANES) has been used to determine prevalence of diabetes in the population. HANES periodically utilizes a probability sample of the U.S. population obtaining data from medical questionnaires, but also, including oral glucose tolerance tests.

2. Provincial Health Care Records

Diabetes should be identified through linkage of records related to physician visits, diabetes supplies including drugs, and hospital discharges. Both primary and secondary diagnoses of diabetes should be utilized.

3. Follow-Up of Survey Repondents

Further information concerning incidence, complications and survival rates should be determined by linking survey cohorts to health and death records.

4. Death Certificate Data

Information based on underlying and contributing causes of death where diabetes is mentioned should be compiled.

By using centralized health records and linkage, extensive data collection can be carried out.

Advantages

This methodology will provide the best estimates of prevalence, mortality and to a lesser extent incidence, free from selection biases inherent in clinical surveys.

Disadvantages

1. There is a lack of uniformity in routinely available health records.
2. Population-based surveys are costly.

B. Local Studies

1. New Registries

New registries can provide important information concerning (a) incidence, (b) costs, (c) case-control studies for etiological factors, (d) cohort studies for complications and morbidity.

The diagnosis of diabetes should be standardized using either the National Diabetes Data Group or WHO recommendations.

There is a unique opportunity for provincial governments to play a major role in diabetes registries. The Prince Edward Island Registry serves as an example where the provision of services and/or supplies through a provincial health care plans has been utilized to collect information. Coordination and standardization between provinces would be essential for these registries to be successful and provide the information that is important for health care planning.

2. Investigator-Initiated Etiologic Studies

Cohort and case-control studies should be conducted in multiple local areas. Studies that should be considered include: examination of ethnic origins (e.g. country of birth, North American Indians), review of seasonal incidence rate differences, viral illnesses, HLA typing, socio-economic background, urban versus rural environment, occupation, diet, and physical activity.

3. Examination of Differences Between type 1 and type 2 Diabetes

The risk of complications for both types of diabetes and the relation to economic factors, childhood antecedents, obesity, family history and previous history of gestational diabetes should be established.

4. Mortality Rates and Causes of Death

A comparison of rates and causes of death in type 1 and type 2 diabetes is in need of urgent review.

5. Review of Risk Factors for Vascular Complications

The specific roles of hyperglycemia, hypertension, hyperlipidemia, diet, exercise, obesity, smoking and other risk factors, need to be evaluated in careful epidemiological studies.

6. Assessment of Diabetes Management

A review of natural history of diabetes and assessment of existing intervention strategies that will allow new programs to be developed for treatment of diabetes and its complications.

EPIDEMIOLOGY OF DIABETES MELLITUS

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Introduction

Diabetes mellitus is a major chronic disease (or group of diseases) with a large impact throughout the world. Diabetes is characterized by chronic hyperglycemia, and after sufficient duration of the disease, by specific microvascular complications involving the eyes and kidneys, by peripheral and autonomic neuropathy, and by nonspecific macrovascular complications involving the heart and peripheral blood vessels. These complications account for the majority of morbidity and mortality associated with diabetes.

In 1980 the World Health Organization (WHO) adopted a classification of diabetes and other categories of glucose tolerance (1). The two common types of diabetes are type 1, or insulin-dependent diabetes (IDDM), and type 2, or non-insulin-dependent diabetes (NIDDM). Impaired glucose tolerance (IGT) designates an intermediate class with glucose tolerance between normal and diabetic. Although persons with IGT are at increased risk of developing diabetes, they rarely show any of its specific manifestations and are not considered to have the disease.

Patients with IDDM are prone to die of ketoacidosis if not treated with exogenous insulin, they usually have antibodies to pancreatic islet cells at the time of diagnosis, and the onset of symptoms is usually sudden. There is little or no endogenous insulin secretion, and the basic physiologic problem is lack of insulin. In contrast, those with NIDDM do not require exogenous insulin for survival, have no islet cell antibodies, and produce endogenous insulin. In NIDDM the basic physiologic problem, while not precisely known, probably involves insulin resistance and inappropriate insulin secretion. In North America and Europe, approximately 90% of people with diabetes have NIDDM, and NIDDM is almost exclusively the type of diabetes found in some populations such as American Indians.

In addition to a new classification, new diagnostic criteria for diabetes and IGT were adopted by WHO and are now widely used. The diagnosis of diabetes may be established by a casual plasma glucose concentration of at least 200 mg/dl (11.1 mmol/l) or the presence of fasting plasma glucose concentrations of at least 140 mg/dl (7.8 mmol/l) on more than one occasion, or by oral glucose tolerance tests meeting the criteria shown in Table 1. IGT is diagnosed when the criteria for diabetes are not met, but the 2 hour post-load glucose is between 140 and 199 mg/dl.

Table 1
World Health Organization Criteria for Classification of Glucose Tolerance

	PLASMA GLUCOSE mg/dl (mmol/l)		
Class	**Fasting**		**Two-hour**
Normal*	less than 140 (7.8)	and	less than 140 (7.8)
IGT	less than 140 (7.8)	and	140-199 (7.8-11.0)
Diabetes	greater than or equal to 140 (7.8)	or	(greater than or equal to 200 (11.1)

* While WHO does not define a "normal" OGTT, the term is used here to include subjects who do not meet criteria for diabetes of IGT.

Two measures of disease frequency will be used in this paper. The prevalence of a disease is the fraction of a population having the disease at a given time, usually expressed as a percentage. The incidence rate, or rate of development of disease, is the number of new cases of disease occuring in a specified population at risk per unit time. Prevalence rates are useful for expressing the amount of existing disease in a population, whereas incidence rates indicate the rate at which new cases appear and are also useful in studying risk factors for a disease. Demonstration that a certain attribute is a risk factor for a disease is, in general, best determined by showing a higher incidence rate in persons with the factor than in those without it.

PREVALENCE OF DIABETES IN THE UNITED STATES

The prevalence of diabetes in the U.S. has been estimated by the Second National Health and Nutrition Examination Survey (NHANES II), conducted from 1976-1980 (2). A representative sample of the U.S. population was studied. Subjects were asked if they had diabetes diagnosed by a physician. Oral glucose tolerance tests were administered to those without a medical history of diabetes, and diabetes was diagnosed by WHO criteria. Although the response rate of subjects selected for glucose tolerance testing was low, preliminary diabetes prevalence estimates have been made. The potential for bias introduced by the incomplete sampling is currently under investigation, but is not thought to be substantial. The estimates of the prevalence of diabetes (sum of previously and newly diagnosed) are shown by age, sex, and race in Table 2. Among U.S. residents aged 20-74 years, an estimated 6.8% (6.4% of the whites and 9.9% of the blacks) have diabetes. The prevalence of diabetes increases with age and is higher in women and in the black population. An estimated 9.8 million U.S. residents between the ages of 20-74 years have diabetes, but only about half of these cases (4.9 million persons) have been diagnosed. The prevalence of IGT is even higher, at 11.2% (10.7% in whites and 12.7% in blacks). While we are unaware of similar statistics for Canada, if the U.S. age-sex-specific prevalence rates for white U.S. residents were to be used as estimates and applied to the 1980 Canadian census, there would be approximately 868,000 Canadians with diabetes and 1.49 million with IGT between the ages of 20-74 years. Thus in terms of numbers of people affected, diabetes might be a very important problem in Canada, as well as in the United States.

Table 2
Total Prevalence of Diabetes* in the U.S. Population Aged 20-74 Years, NHANES II, 1976-80 By WHO Criteria

Age:	20-74	20-44	45-54	55-64	65-74
Race and Sex			**Percent of Population****		
All Races	6.8	2.0	8.5	13.4	18.7
Male	5.9	1.4	7.9	9.9	20.1
Female	7.7	2.5	9.1	16.4	17.4
White	6.4	1.7	8.2	12.5	17.9
Male	5.5	1.0	7.8	9.4	19.1
Female	7.3	2.2	8.7	15.2	17.0
Black	9.9	3.2	12.9	22.5	26.4
Male	8.6	2.8	11.1	14.6	29.4
Female	11.0	3.5	14.6	27.9	24.1

*Sum of percent of persons with a physician-diagnosed medical history of diabetes and of undiagnosed diabetes using WHO criteria.

**Standard errors cannot be calculated because the rates of undiagnosed diabetes are based on a subsample of persons from which the rates of diagnosed diabetes are derived.

It is thought that the frequency of diabetes is probably increasing in the U.S. The rate at which new diagnoses of diabetes were reported by respondents to the U.S. Health Interview Survey increased from 1936 until about 1973, after which it has tended to remain stable (3). Similarly, according to surveillance of medical records in Rochester, Minnesota, the incidence rate of physician-diagnosed cases increased by 95% in men and 77% in women from 1945 through 1954 (4). During the next 15 years the rate of increase lessened, and then the incidence decreased. Much of this change was attributed to improved case ascertainment due to greater access to medical care and widespread use of automated blood glucose analysis. Despite the probable increase in diabetes ascertainment, it is still estimated that only about half of those with diabetes in the U.S. are diagnosed.

INCIDENCE AND RISK FACTORS FOR IDDM

IDDM is usually characterized by an abrupt onset of symptoms, insulinopenia and dependence on injected insulin to sustain life. Classically believed to be a disease with an onset at an early age, it can occur for the first time in adults. The incidence is well established in childhood and adolescence. In the U.S., the incidence up to 20 years of age is about 14 cases/100,000 person-years (5,6). Rates in the black population are about one third to one half lower than those in whites. The disease has a peak incidence around puberty. Beyond 20 years of age the incidence is open to considerable doubt. While it has long been thought that IDDM has a lower incidence in adults than in children, there is little evidence for this belief. In a report of the incidence of diabetes by clinical type in Rochester, Minnesota, Melton et al (7) found the incidence of IDDM to vary little with age (Figure 1).

Evidence of genetic determinants for diabetes was first provided by twin studies. When at least one of a pair of twins had diabetes, the rates of concordance were higher for monozygotic than for dizygotic twins (8,9). While in these studies IDDM and NIDDM were not distinguished, even among the juvenile patients reported by Harvald and Hauge (8), most of whom may have had IDDM, concordance was higher in monozygotic than in dizygotic twins.

In the last decade evidence of genetic susceptibility in IDDM focused around its relationships with various markers in the HLA region of chromosome 6. In Canada, Singal and Blajchman (10) and in Denmark, Nerup et al (11) reported excessive frequencies of HLA-B8 and HLA-Bw15 in young diabetic subjects treated with insulin. Subsequently, relationships between IDDM and the HLA-DR locus were found to be much stronger, particularly with DR3 and DR4. Furthermore, the occurrence of IDDM is much more frequent in HLA-DR3/DR4 heterozygotes, with an estimated risk of over 40 times that of those with neither of these antigens (12). These data suggest that IDDM susceptibility genes are closely linked to the HLA-DR locus or that particular HLA-DR antigens by themselves cause susceptibility to IDDM. In view of the excess risk of diabetes in the DR3/DR4 heterozygotes, there appear to be two or more diabetes susceptibility alleles in this region.

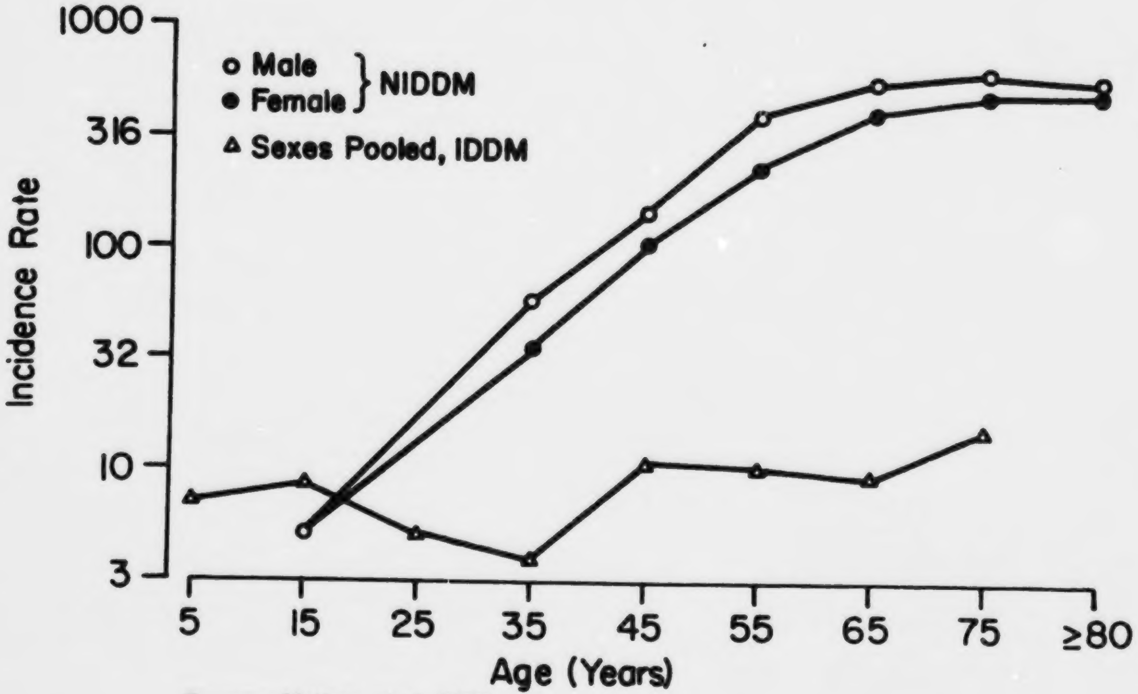
The risk of a sibling of a patient with IDDM developing diabetes by age 20 is about 3-5% (13, 14, 15, 16). The risk of developing IDDM in the HLA-identical sibling of a diabetic, particularly when DR3/DR4 heterozygous, is not known, but has been estimated to be about 90 times that of the general population (17). Longitudinal studies are underway to quantify such risks. In the Barts-Windsor study in England, 5% of siblings of diabetic probands, with an average age of 16 years, had IDDM. Rates were 1, 4, and 14% in siblings sharing none, one, or both HLA haplotypes with the propositus (17).

In the past it was generally assumed that the development of IDDM was usually a rapid process, with the development of marked hyperglycemia shortly after its onset. This assumption was challenged by the discovery that islet cell (cytoplasmic) antibodies are present in the sera of the majority of patients with IDDM at the time of or shortly after diagnosis (18, 19). This gave rise to the concept that islet cell antibodies may act as a marker for beta cell destruction and these could, therefore, be present before IDDM was recognized.

This hypothesis was examined in the Barts-Windsor Prospective Family Study, in which 12% of the siblings of propositi with IDDM and 7% of their parents had islet cell antibodies (20). These antibodies were of the complement fixing type in 4% of the siblings and 2% of the parents. Over a 3-year period, seven persons developed diabetes, of whom six had had complement fixing islet cell antibodies for between 3 and 36 months prior to the onset of diabetes. In a subsequent report from this study, among 20 first-degree relatives of patients with IDDM with complement-fixing islet cell antibodies and followed for at least 5 years, twelve remained asymptomatic (21). One of these had been persistently antibody positive for 5 years, and the others had varying degrees of persistence. Eight became diabetic (seven of whom were insulin dependent), confirming the high risk associated with islet cell antibodies, yet showing that progression to IDDM, at least within several years, was not inevitable. Another prospective study of 24 monozygotic twin pairs initially discordant for IDDM found that four twins subsequently developed IDDM (22). Three of these twins developed islet cell antibodies and pancreatic islet cell dysfunction years before development of overt diabetes. Only two of the 20 nondiabetic twins developed islet cell antibodies, but the length of follow-up of these two twins was only 1.5 years.

Evidence for a latent period in IDDM has been provided not only by islet cell antibodies, but also by the finding that some children have glucose intolerance for an appreciable period of time before developing acute symptomatic manifestations of IDDM (23). These observations provide further evidence of a long latency of IDDM and suggest that both islet cell antibody positivity and glucose intolerance have predictive value, and that the early phases of IDDM are much more prolonged than previously suspected.

FIGURE 1



Source: Melton, et al, 1983

Figure 1. The incidence of diabetes (in new cases/100,000 person-years) by clinical type in Rochester, Minnesota, 1945-69. Incidence rates, on logarithmic scale, are shown for the development of insulin-dependent diabetes mellitus (IDDM) and for non-insulin-dependent diabetes mellitus (NIDDM) by decades of age. The midpoints of the age groups are shown. From Melton, et al, 1983 (7).

As only about half of pairs of identical twins with IDDM are concordant, environmental factors must also play an important role in the pathogenesis of the disease. Whether such factors operate only in genetically predisposed individuals is unknown. Evidence of environmental precipitants of IDDM includes seasonal variation in incidence, with peak attack rates in the winter months (24), suggesting that certain viral infections are causal factors. Evidence that such viruses in animals can lead to pancreatic destruction and hyperglycemia is well established. In humans, however, the evidence is less compelling. Higher frequencies of neutralizing antibody titers to Coxsackie B4 were found in patients with IDDM than in controls (25). Coxsackie virus antibodies were more common in patients with newly diagnosed IDDM if their HLA types were HLA-B8 or HLA-Bw15 (26). Coxsackie B4 virus was isolated from the pancreas of a child dying with IDDM of recent onset (27). Mumps may be more common in children before the onset of IDDM (28). However, the majority of children with IDDM do not show evidence of recent infection by these common viruses. Furthermore, it may be, even in the well-documented instances, that the effect of the virus was simply to add further insult to a pancreas already compromised by immunological destruction and precipitate clinical disease. Nevertheless, the hypothesis that some viruses may initiate immunologically mediated beta-cell destruction remains attractive.

INCIDENCE OF NIDDM IN THE UNITED STATES

Table 3 summarizes incidence studies of NIDDM in the United States and selected incidence studies elsewhere. NIDDM incidence rates in Rochester, Minnesota, in relation to age and in comparison with IDDM, are shown in Figure 1. In most population studies, however, the incidence of IDDM and NIDDM cannot be readily distinguished. As illustrated by the Rochester data, where about 3% of those developing diabetes after age 40 had IDDM, the majority of diabetes first occurring in adults is NIDDM. Therefore, in adults, the incidence of NIDDM can be well approximated by the total incidence of diabetes.

The incidence of NIDDM has been generally shown to increase with increasing age (see below). The rates vary according to the age group studied, and in order to correct for the differences in the age range and age distribution among the various studies shown in Table 3, the data have been age adjusted to the 1980 United States population aged 40 years and over. In the studies using only interviews or health records, the reported increase in incidence with age may have been the result of more frequent medical care in older age groups and hence a greater chance of diagnostic tests being performed, rather than representing a true increase in incidence with age.

The large variation in rates shown in Table 3 may, to a large extent, be attributable to differences in methods used to determine incidence. For example, in the United States National Health Survey and Health Interview Survey, a questionnaire was used to determine if a diagnosis of diabetes had been made in the last 12 months (29). On the other hand, the results of the Oxford (30), Framingham (31), Tecumseh (32), and Pima Indian (33) surveys depended on the demonstration of a clinical diagnosis or the presence of a diagnostic glucose tolerance test among persons who had had normal glucose tolerance at the baseline examination. Furthermore, even in surveys where glucose tolerance testing was used as the basis for the diagnosis and for establishing that the subject was not diabetic at baseline, the type of test performed and the criteria used to interpret the results vary from study to study. Thus, although the data are presented in a single table, direct comparisons among these studies are hazardous.

RISK FACTORS FOR NIDDM

Age and Sex

Most studies demonstrate an increased incidence of NIDDM with age. In Rochester, Minnesota (Figure 1), the incidence of NIDDM increased with age for both men and women, whereas the incidence of IDDM varied little with age (7). In Pima Indians, however, incidence rates of NIDDM increased in males until age 44 and in females until age 54 and then declined for both sexes (33). In groups with high incidence rates, such as the Pima Indians, it is possible that susceptible individuals may develop the disease at a relatively early age, which may then result in a decline in incidence in the older age groups. It is also possible that older individuals have not experienced the same environmental forces as the younger generations.

There is no clear evidence that gender itself influences the risk for development of NIDDM. Among the rates listed in Table 3, there was no consistent difference by sex.

Race

The incidence and prevalence of NIDDM vary considerably among different racial groups. The highest incidence rates have been reported among the Pima Indians and the natives of the central Pacific island of Nauru (Table 3). Of particular interest in the Nauruans was the greater prevalence of NIDDM among pure Nauruans compared with those with foreign admixture, as determined by HLA types (34). Among Mexican-Americans in Texas, the prevalence of diabetes varied directly with the estimated amount of native American admixture (35). Similarly among the Pima Indian population, those with Caucasian admixture (by history or blood typing evidence) had lower prevalence rates of NIDDM than full-heritage Indians (Knowler, unpublished data). Also, the prevalence of diabetes was greater in full heritage than in mixed heritage Cherokee Indians in North Carolina (36) and Choctaw Indians in Oklahoma (37). Few studies allow adequate comparisons of incidence rates between different racial groups.

Table 3

Incidence Studies Of Glucose Intolerance In Adults

Reference	Population and Study	Diagnostic Criteria	Date	Number of Incident Cases Studied	Age at Diagnosis	Sex	Annual Incidence Per 1,000 Persons	Age-Adjusted* Incidence Per 1,000 Persons Ages 40+ Years
	National Interview Surveys							
a	U S., National Health Survey	Physician-diagnosed diabetes reported in a household interview	1935-36	874	25+	Male Female	.43 .76	.69 1.17
b	U.S., National Health Interview Survey	Same as above	1978	-	All ages	Male Female	1.91 3.37	- -
b	U.S., National Health Interview Survey	Same as above	1979-81	230	20+	Male Female	3.17 3.22	5.53 4.58
	Local Populations, Laboratory/Clinical Criteria**							
c	Oxford, Massachusetts	Glycosuria and postprandial blood glucose greater than or equal to 200; or postprandial greater than 170 with retest greater than 140	1946-60	16	34-55	Both sexes	1.1	
d	Rochester, Minnesota	About 81% diagnosed by fasting blood glucose greater than 110; remainder by 2-hour post glucose greater than 110-140; medical chart review	1945-70	1,099	All ages	Male Female	1.2 1.1	2.0 1.4
e	Employed northeastern Caucasians	Clinical diagnosis, or fasting blood glucose greater than 130 or post-prandial greater than 170	1954-64	249	30-59	Male	6.1	6.7
f	Framingham, Massachusetts	100 g GTT; 1-hour greater than 205, 2-hour greater than 140; or insulin treatment; or oral agents with casual glucose greater than 150	1954-68	274	33-67	Male Female	4.8 3.9	

Table 3 (Continued)

Reference	Population and Study	Diagnostic Criteria	Date	Number of Incident Cases Studied	Age at Diagnosis	Sex	Annual Incidence Per 1,000 Persons	Age-Adjusted* Incidence Per 1,000 Persons Ages 40+ Years
g	Choctaw Indians Full heritage Mixed heritage	Chart review; fasting blood glucose greater than 130, or 2-hour venous blood glucose greater than 150	1956-61	175	All ages	Both sexes Full Mixed	11.1 4.7	20.1 17.5
h	Tecumseh, Michigan	Physician-diagnosed diabetes and insulin or oral use; or diabetes on death certificate; or blood glucose score post 100-gm glucose	1959-79	184	20+	Male Female	2.8 3.0	4.3 5.5
i	Israeli civil servants	Clinical diagnosis; or 1 gm/kg OGTT, fasting greater than or equal to 120, 1-hour greater than or equal to 180, 2-hour greater than or equal to 130	1963-68	373	40+	Male	8.0	9.4
Local Populations, NDDG/WHO Criteria								
j	Pima Indians	75-gm OGTT, 2-hour plasma glucose greater than 200	1965-75	234	5+	Male Female	16.4 20.1	36.1 49.5
k	Nauru, South Pacific	75-gm OGTT, 2-hour plasma glucose greater than 200	1975-82	27	All ages	Male Female	11.0 9.5	16.8 11.3

*Age-adjusted by direct standardization to the 1980 United States population ages 40+ years, except the 1935-36 national survey and Pima Indian study (rates were for ages 35+ years) and the 1979-81 national survey (rates were for ages 45+ years). Cumulative incidence rate method used for Oxford, Israeli, and Nauruan studies, the person-year method in the other studies.

**Glucose concentrations expressed in mg/dl

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Prevalence studies also suggest important differences in the likelihood of developing diabetes among other racial groups in the United States. Mexican-Americans in San Antonio, Texas (38) had a higher sex- and weight-specific prevalence of NIDDM than non-Hispanic Caucasians (Table 4), and, as noted earlier, blacks in the U.S. have higher prevalence rates than whites.

Table 4

Prevalence of NIDDM in Mexican Americans (MA) and Anglo-Americans (AA), By Obesity Level

	MA Males		AA Males		MA Females		AA Females	
Obesity Category	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Lean	6/87	6.9	1/55	1.8	2/83	2.4	0/76	0
Average	9/128	7.0	2/55	3.6	9/124	7.3	0/77	0
Obese	24/166	14.5	1/56	1.8	38/334	11.4	6/79	7.6
Overall	39/381	10.2	4/166	2.4	49/541	9.1	6/232	2.6
Ratio MA/AA		4.02				2.41		

Source: Stern, MP, SP Gaskill, HP Hazuda, et al. Does obesity explain excess prevalence of diabetes among Mexican Americans? Diabetologia 24:272-77, 1983 (38).

Genetic Risk Factors

Diabetes has long been suspected to have a genetic basis, but early studies attempting to elucidate the mechanism of inheritance failed to make the distinction between IDDM and NIDDM. These studies, however, did show familial aggregation of diabetes, and higher concordance rates among twins were reported when the disease had a later rather than an earlier age of onset. Given that NIDDM characteristically has an onset in middle-age or beyond, that the frequency of the disease may have increased in recent years, and that many relatives of diabetics are assumed to carry an unrecognized genetic susceptibility to diabetes, the traditional methods of segregation analysis to determine the mode of inheritance of NIDDM have been fraught with difficulties.

The presence of NIDDM in different frequencies among different racial groups and in intermediate frequencies among mixed racial groups, all living in the same environment, is most easily explained on a genetic basis. Such data, however, give no evidence of the mode of inheritance. Studies of diabetes within families, in twins, and in association with genetic markers have attempted to determine the genetic risk factors for NIDDM.

Family Studies. A large family study in Canada demonstrated empirically the risks of diabetes among first degree relatives of subjects with diabetes and compared them with disease prevalence in the population of Prince Edward Island (Table 5) (15). In the Pima Indians of Arizona, parental diabetes was a strong risk factor for diabetes.

Even after controlling for age and obesity, Pimas with two diabetic parents had about four times the incidence rate of diabetes as those with two nondiabetic parents (39).

Twin Studies. In a study of 200 pairs of monozygotic twins in whom diabetes had been diagnosed in at least one twin, the likelihood of diabetes being present in the other twin was much greater in the pairs in which NIDDM, rather than IDDM, was present (40). Among twin pairs the concordance rate was 91% for those with NIDDM, compared with 54% for those with IDDM. The high concordance among monozygotic twin pairs with NIDDM suggests an important genetic contribution to the disease.

Genetic Markers. Information about the genetics of a disease may be obtained if the disease can be shown to be associated with or linked to other genetically determined characteristics. Associations are detected in population samples of subjects with and without the disease, whereas linkage is demonstrated within pedigrees.

We are unaware of systematic studies of genetic linkage between the HLA system and NIDDM, and no particular HLA marker has been consistently associated with NIDDM. In several populations, however, modest associations have been found, including HLA-A2 among the Pima Indians (41) and the Xhosa of southern Africa (42), HLA-Bw56 in Nauruans (34), and HLA-Bw61 among Fiji Islanders (43). The frequencies of polymorphic DNA insertion sequences near the human insulin gene were found to differ between subjects with and without NIDDM when data from whites, blacks, and Pima Indians were combined (44), but no significant association was found among Nauruans (34) or among full-heritage Pima Indians (45).

The discovery that the human genome may be mapped using highly polymorphic DNA insertions makes it likely that linkage studies will be used to determine the chromosomal location of genes conferring diabetes susceptibility. The application of such techniques to families with NIDDM in two or more generations now seems to be the most likely method through which genes conferring susceptibility to NIDDM will be recognized and by which the mode or modes of inheritance of the disease will be clarified.

Metabolic Risk Factors

Glucose Concentration. An elevated plasma glucose concentration has consistently been found to be strongest predictor of subsequent deterioration to NIDDM; the higher the glucose the greater the likelihood of developing diabetes (30, 46, 31, 47, 48, 49, 50). Most people with IGT, however, do not rapidly progress to diabetes. In a 10 year follow-up of individuals with glucose intolerance who approximately met the WHO criteria for IGT, 15% worsened to diabetes, but 53% had substantial improvements in glucose tolerance (51).

Table 5
Percent of Relatives With Diabetes And Relative Age-adjusted Prevalence of Diabetes in Living Relatives of Diabetic Probands Compared With The Prevalence of Diabetes in Prince Edward Island, Canada

	Age at Onset of Proband (Years)					
	Diabetic Male Probands			Diabetic Female Probands		
Relatives	0-19	20-39	40	0-19	20-39	40
Fathers (N = 2,883)						
Percent diabetic	2.7	5.1	14.8	3.3	7.6	8.6
Relative prevalence	2	2	4	3	3	3
Mothers (N = 3,378)						
Percent diabetic	0.9	7.7	14.4	2.3	7.4	9.7
Relative prevalence	2	2	3	2	2	2
Brothers (N = 8,830)						
Percent diabetic	2.5	4.0	8.0	2.2	3.2	7.1
Relative prevalence	14	5	4	11	4	3
Sisters (N = 8,992)						
Percent diabetic	1.8	3.4	5.0	3.1	4.2	6.8
Relative prevalence	10	4	2	13	4	2
Sons (N = 5,162)						
Percent diabetic	2.6	1.5	0.7	1.4	0.7	1.4
Relative prevalence	40	13	3	20	6	3
Daughters (N = 5,145)						
Percent diabetic	2.5	0.6	0.9	1.1	1.2	0.7
Relative prevalence	41	7	2	18	9	1

Source: Simpson, N. Diabetes in the families of diabetics. Can Med Assoc J. 98: 427-32, 1968 (15).

Knowledge of the relationship of glucose concentration to the subsequent occurrence of diabetes has led to at least three attempts to determine if pharmacologic and diet intervention can reduce the rate of development of NIDDM. In a randomized clinical trial in Sweden, none of those with abnormal glucose tolerance who were randomly assigned to dietary and tolbutamide therapy and could be shown to have complied with the tolbutamide therapy (about half of those initially assigned to this group) developed diabetes over a 10 year period (Table 6) (52). All of the groups with a prescribed intervention, however, had a lower incidence of diabetes than the untreated control group. While those who continued tolbutamide may have been self-selected, analysis of the group by original assignment showed no significant difference in the incidence of diabetes between those assigned to tolbutamide and diet and those assigned to diet alone, but the incidence in these groups considered together was significantly lower than in those who received no treatment assignment. Tolbutamide may have had an effect, but it is also possible that diet and increased surveillance, with or without tolbutamide, may have been benefical.

Table 6
Development of Diabetes During 10 Years Among Swedish Persons With Impaired Glucose Tolerance, By Treatment

Treatment Group	Number	Percent
Diet plus continued tolbutamide	0/23	0
Diet plus discontinued tolbutamide	5/26	19
Diet plus continued placebo	4/26	15
Diet plus discontinued placebo	2/22	9
Diet alone	7/50	14
No therapy	17/59	29
Normal glocuse tolerance	0/52	0

Source: Sartor, G., B. Scherstén, S. Carlström, A. Melander, A Nordén, and G. Persson. Ten year follow-up of subjects with impaired glucose tolerance. Diabetes 29:41-49, 1980 (52).

Two other small studies have also examined the effects of oral hypoglycemic agents in patients with impaired glucose tolerance. In contrast to the Swedish study, in Bedford, England, 10 year treatment of subjects with IGT with tolbutamide and diet failed to reduce the incidence of diabetes (51). In the Whitehall Study in England, there was no difference in those treated with dietary restriction and those receiving treatment with phenformin in the 10-year cumulative incidence of diabetes (49). As IGT appears to be the strongest risk factor for NIDDM, more studies are warranted to determine if appropriate intervention can prevent the development of NIDDM.

Insulin Concentration. Although IDDM is primarily the result of a failure to secrete insulin, NIDDM is characterized by resistance to insulin-mediated glucose disposal, and the disease becomes manifest when insulin secretion is inadequate to compensate for the degree of resistance.

In Japanese subjects, a diminished ratio of insulin to glucose concentrations following oral glucose predicted the development of diabetes over 5-12 years (53). In Bedford, England, deterioration to diabetes among those with IGT was not significantly related to changes in insulin concentration after the effect of glucose concentration was accounted for by logistic regression analysis (49). Among Pima Indians with normal glucose tolerance, those with higher serum insulin concentrations, relative to their two-hour post-load plasma glucose concentrations, were at greater risk of deterioration in glucose tolerance, whereas among those with IGT, those with lower insulins relative to their glucose concentrations were at greater risk of deterioration (54). These findings in the Pimas suggest that among those with normal glucose tolerance, relative hyperinsulinemia (suggesting insulin resistance), and among those with IGT, relative hypoinsulinemia (suggesting impaired insulin secretion), are risk factors for NIDDM.

Obesity. Obesity is a strong risk factor for NIDDM. In Oslo, Norway (55) there was a positive relationship of obesity and 10 year diabetes incidence in 40 to 49 year old males (Figure 2). Body mass index (weight divided by the square of height) was a risk factor for NIDDM in Pima Indians, as shown in Figure 3 (39). Among thirteen thousand predominantly Caucasian male executives in the Northeastern United States, increased relative weight predicted diabetes (46), as it did also in Framingham, Massachusetts (31). In the Pima Indians, obesity was much more predictive of development of diabetes when at least one parent had diabetes than when neither parent had diabetes (39). Similarly in Oxford, Massachusetts, obesity predicted diabetes only when family history was also positive (30).

The distribution of adiposity may also play a role in determining the risk of development of NIDDM. In a nationwide U.S. study of women participating in a weight reduction program, a greater waist to hip ratio, indicating a more central distribution of adiposity, was positively associated with diabetes prevalence, regardless of degree of obesity (56). Similar findings have been reported for men and women in California (57), France (58), and among Mexican-Americans (59).

While weight reduction is widely recognized as a means of decreasing plasma glucose concentrations in NIDDM (60), it remains to be demonstrated that weight reduction will diminish the incidence of NIDDM in the obese or others at high risk of developing the disease.

Plasma Lipids. Hyperlipidemia is associated with both diabetes and obesity. But are elevated lipids predictive of diabetes independently of obesity? Relationships between serum cholesterol, very low density lipoproteins (VLDL), and triglyceride concentrations, independent of obesity, and the incidence of NIDDM have been reported. In a 5 year incidence study of NIDDM in Israeli men, total serum cholesterol and LDL cholesterol were postively, and HDL cholesterol negatively, associated with future diabetes, but after control for confounding variables, only the relationship with total cholesterol remained significant (61). In adult males of the Northeastern United States, serum cholesterol predicted diabetes (46), but in Tecumseh, Michigan (32) and in middle-aged males in Oslo, Norway (62) cholesterol was not a predictor of diabetes independent of other factors. Elevation of VLDL-cholesterol, but not LDL-cholesterol, predicted NIDDM in Framingham, Massachusetts (31). In Nauruan males, but not females, fasting triglycerides showed a weak association with the onset of NIDDM (63). In the prospective Paris study of male civil servants, diabetes incidence was 3.5 times as great in those whose serum triglyceride concentrations were in the highest tertile as in those in the lowest tertile, but this association was not apparent after adjustment was made for blood glucose (50).

Blood Pressure. Hypertension was more common among DuPont Corporation employees in the U.S. who became diabetic than in age, sex and geographically matched controls (64). This relationship was found across four ranges of obesity, suggesting that blood pressure had an effect in addition to that of obesity. Systolic blood pressure predicted NIDDM in U.S. college males, but only in the higher weight group (65). In the Whitehall and Bedford Surveys, blood pressure adjusted for age and obesity was greater in newly diagnosed diabetics (66), but in follow-up of those with IGT, blood pressure did not predict subsequent diabetes in either survey (49, 51). Among studies using multivariate analyses, only among Israeli male civil servants did blood pressure predict NIDDM when adjustments were made for other associated variables such as age, body mass index, and education (61).

Peripheral Vascular Disease. Peripheral vascular disease is usually considered a complication of diabetes, but two incidence studies have found it to be a risk factor for diabetes. A history of intermittent claudication was a risk factor in Framingham, Massachusetts (31) and in the Israeli civil servants study (61). It is possible that the relationship may not be a direct one, but that there are common risk factors for both diabetes and peripheral vascular disease. Similarly, joint risk factors may exist for diabetes and other associated conditions such as hyperlipidemia and hypertension.

Drugs and Chemical Agents. Many drugs affect glucose tolerance and may precipitate diabetes in susceptible subjects. The risks associated with exposure to specific drugs, however, are poorly understood, even for those used frequently. An extensive list of drugs and other chemical agents that have been reported to be associated with diabetes and glucose intolerance was published by the National Diabetes Data Group (67).

FIGURE 2

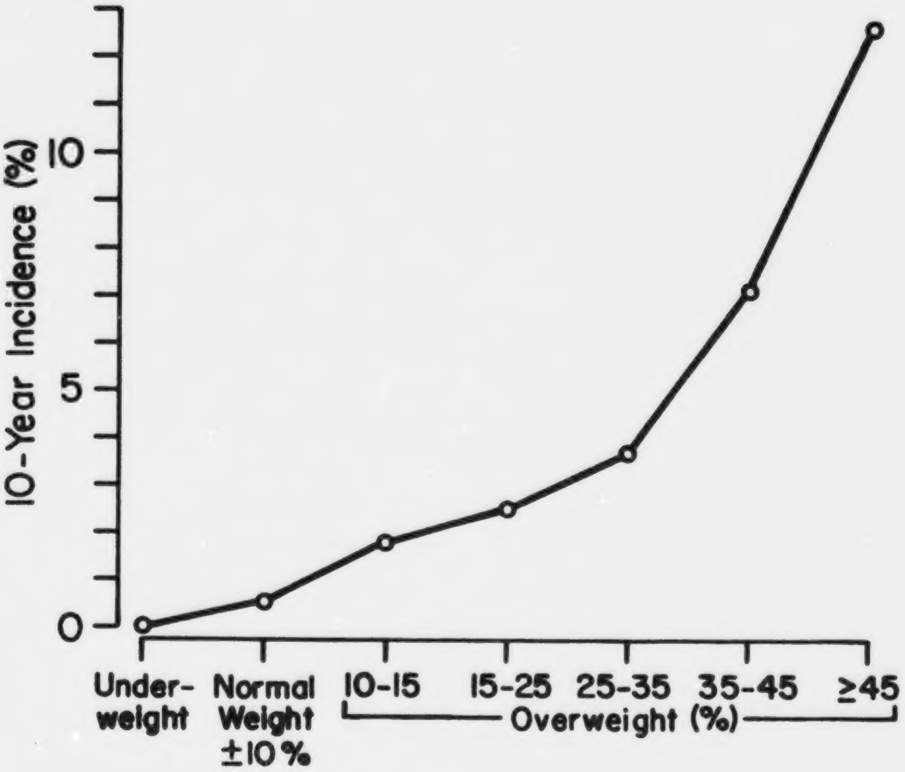

Figure 2. Cumulative 10-year incidence (in per cent) of clinically diagnosed diabetes according to relative body weight in men, initially 40-49 years of age, in Oslo, Norway. From Westlund and Nicolaysen, 1972 (55).

FIGURE 3

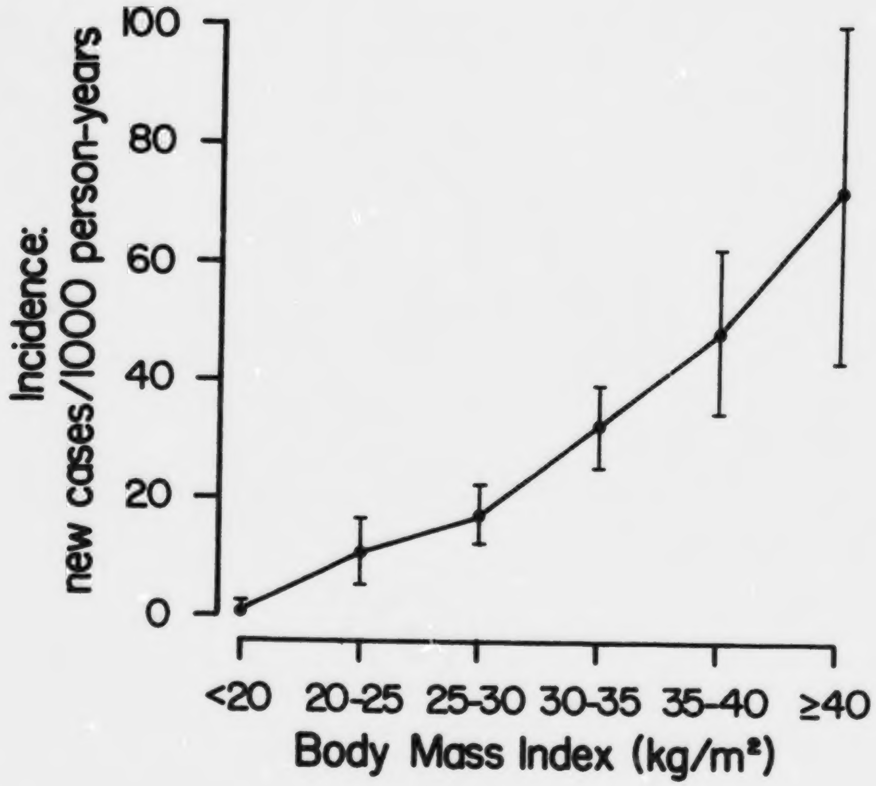

Figure 3. Age-sex adjusted incidence of diabetes, diagnosed by WHO criteria, by body mass index (weight divided by the square of height) in Pima Indians. Incidence rates are in new cases/1000 person-years and are shown with 95% confidence intervals. From Knowler et al, 1981 (39).

Other Metabolic Risk Factors. Increased risks of development of NIDDM have been reported, in single studies, for elevated uric acid (61), low hemoglobin (31) and diminished vital lung capacity (65).

Environmental Risk Factors and Lifestyle

Migration Studies. Migration and rapid changes in lifestyle are associated with the emergence of NIDDM in populations, sometimes in exceptional frequencies. Studies of migrants offer the opportunity to compare the effects of a change in lifestyle, and they permit comparisons of disease prevalence among different racial groups who come to live in the same location. Changes in lifestyle associated with migration often involve the development of obesity, reduction in caloric expenditure, and changes in diet towards one with lower fiber content and a higher proportion of fat and refined carbohydrates. For example, the age-sex adjusted prevalence of diabetes was greater in Japanese migrants to Hawaii (12.3%) than in residents of Hiroshima, Japan (6.9%) (68). Caloric intake was similar, but the migrants were more obese, ate a diet containing a higher proportion of fat and simple carbohydrates and were more sedentary. The relative importance of these factors to development of NIDDM may vary among populations and may depend on the degree of genetic susceptibility.

Asian Indian migrants to many areas of the world have higher prevalence rates of NIDDM than the population residing in India (69). The socioeconomic status of expatriated Indians is frequently higher than that of those in India, and diet, exercise patterns, and obesity also change. Migrant Indians generally have higher prevalence rates of NIDDM than the predominant racial group in the host country. Environmental factors alone do not appear to account for these differences, so it is presumed that Indians may be more genetically susceptible to diabetes than are many other populations.

In many developing countries, migrations within the country permit comparisons between those living in an urban and a rural environment. In comparing urban and rural populations, higher prevalence rates have frequently been demonstrated among the urban population. These differences are usually interpreted as indicating the effects of environmental factors, such as changes in dietary habits, physical activity, and socio-economic factors, on the expression of the disease.

Rural Asian Indians have lower prevalence rates of diabetes than their urban counterparts (69). Among the Micronesian population of Kiribati (formerly the Gilbert Islands), the age adjusted prevalence rates of NIDDM were over twice as high in urban as in rural residents (70). Greater obesity in the urban population did not alone explain the rural-urban difference in prevalence. In Puerto Rico, the length of time since migration from rural to urban areas within the island did not appear to influence the greater prevalence of diabetes among urban dwellers, although rural residents had lower rates of diabetes than urban residents (71).

Modernization. In some populations the way of life has changed dramatically over a short time period, resulting in marked changes in the frequency of diabetes and thus providing strong evidence that environmental determinants may influence expression of the disease.

Guam, the chief island of the Marianas, has undergone considerable change to a more Western way of life since the end of World War II. Inhabitants of Guam have a higher prevalence of NIDDM (males 10%, females 13%) than the inhabitants of Rota, a more traditional Marianas island (males 3%, females 8%). Migrants to California from these islands have rates (males 10%, females, 14%) similar to those of the residents of Guam (72).

Diabetes was rarely noted in the literature describing the health conditions of the Pima Indians in the early 1900s. Since acquiring a more Western style of living, they have developed the highest known prevalence and incidence rates of diabetes (33). Age-adjusted prevalence rates of NIDDM among the Pima Indians increased 42 percent in the ten years preceding 1977 (73). Obesity also increased during this period. A similar change may have taken place in the population of Nauru, which, within a brief period, has developed one of the highest per capita incomes and the second highest prevalence of diabetes in the world (63, 74). Prevalence rates are also higher among Polynesians, Micronesians, and Australian Aborigines who have adopted a Western style of living than those who have retained their traditional ways of living (75).

Migrant studies, along with the demonstration that diabetes tends to be frequent among populations who have undergone rapid changes in lifestyle, provide a large body of circumstantial evidence that such changes are associated with the emergence of NIDDM, sometimes in exceptional frequencies. The specific determinants, however, are uncertain. Such changes in the way of life are often associated with the development of obesity, reductions in caloric expenditure, and changes in diet towards one with a reduction in fiber content and a higher proportion of fat and refined carbohydrates. Which of these changes are responsible for the development of NIDDM is uncertain, and it may be that all of them, or some other as yet undetermined factors, are responsible for the increases. A combination of these factors seems likely to play a role, but the relative importance may vary among populations and may depend on the degree (and possibly type) of genetic susceptibility in the populations. It is of interest that when diabetic Australian Aborigines returned to their traditional lifestyle as hunter-gatherers for 7 weeks, during which time they lost weight, exercised more, and ate a low fat diet, their glucose tolerance was markedly improved (76).

Socio-economic Status. In some economically developing countries (particularly in India), the wealthy are more likely to have diabetes (77, 78,) than the poor, while in the United States, according to the National Health Interview Survey, the poor have the highest prevalence of diabetes (Harris, M.I., personal communication). In Tecumseh, Michigan, less formal education was found to be a risk factor for diabetes only in men and women aged 20 to 39 (32).

Physical Activity. There is little information about exercise and the risk of NIDDM. Trained athletes have been reported to have lower insulin responses to glucose infusion than nondiabetic controls (79). Training appears to diminish insulin resistance (80), while enforced bed rest reduces glucose tolerance by increasing insulin resistance (81). Diabetes prevalence among Fiji islanders of different races was related to their levels of physical activity (69). The measurement of physical activity in populations, however, is difficult, and good studies using precise and reliable measures are required.

Diet. Excessive energy intake as a cause of diabetes was inferred from decreased hospitalization and mortality rates for diabetes during times of food shortages such as during war (82). The decrease in diabetes mortality rates in several cities during World War I was attributed to a high carbohydrate, low fat diet as well as to diminished caloric intake (83). But in the only incidence study that examined this issue among large numbers no relationship was found between energy intake (or any other aspect of dietary history) and subsequent development of NIDDM (61).

Dietary constituents as risk factors for NIDDM are particularly difficult to evaluate because of unreliability of dietary recall and because the major postulated risks -- low intake of starch and fiber, high intake of sucrose and highly processed carbohydrates, and high intake of fat -- are often strongly correlated with each other. Japanese migrants to Hawaii had approximately twice the rate of NIDDM as their counterparts in Hiroshima. They also ate approximately twice as much fat, one-third less complex carbohydrate, and almost three times as much simple carbohydrate (68).

West (82) reported that 21 studies suggested excessive sucrose was a risk factor for diabetes and 22 studies suggested it was not. More recently in a prospective study of 213 initially non-diabetic Pima Indian women, significantly higher rates of NIDDM subsequently occurred in those women who ate larger amounts of starch and total carbohydrates, but not sucrose or other dietary components (84). On the other hand, inter-population comparisons have shown a negative correlation between the per cent of calories consumed as carbohydrate and the prevalence of diabetes (85).

Risk Factors for NIDDM Associated with Pregnancy

Gestational Diabetes. In the United States there is little relationship between parity and subsequent NIDDM (86), but women with gestational diabetes which reverted to normal post-partum were found to be at greater risk of subsequent development of NIDDM than women without gestational diabetes (87). In nondiabetic Pima Indian women, the degree of glucose intolerance during pregnancy was predictive of subsequent NIDDM (88).

Intrauterine Environment. The intrauterine environment influences onset of NIDDM in offspring. In Pima Indians, offspring of mothers who were diabetic during pregnancy had a higher risk of developing obesity and NIDDM than offspring of mothers who later developed diabetes (89, 90). The risk for NIDDM persisted after controlling for parents' age of onset and fathers' diabetes, suggesting that in the diabetic mother, the intrauterine environment has an effect on the appearance of diabetes which is additional to that of genetic effects.

MORBIDITY, MORTALITY, AND COSTS OF DIABETES

Morbidity

The two major types of diabetes share a common set of symptoms and sequelae, although the relative frequency and severity of these disease manifestations may differ between the types and between different segments of the diabetic population for a variety of reasons. The classical symptoms of diabetes -- polyuria, polydipsia, hunger, and weight loss -- are directly attributable to the hyperglycemia of diabetes. Refractive changes in the eye are another acute consequence of hyperglycemia. These acute complications are readily reversible by re-establishing metabolic control.

The metabolic derangements also influence many other processes. For example, the ability of the white blood cells and macrophages to kill bacteria is compromised, and thus the patient with hyperglycemia is likely to develop a variety of infections, such as urinary tract infections, cellulitis and vaginitis, as well as being more susceptible to other chronic infections, such as tuberculosis.

Occasionally the patient with NIDDM will develop diabetic ketosis or lactic acidosis. These two rare metabolic complications usually develop only in the presence of stressful events, such as myocardial infarction or severe infections. Diabetic ketoacidosis is much more characteristic of IDDM, where it may be the inital presenting illness, or may develop if insulin treatment is stopped or is inadequate.

A number of complications of pregnancy are directly associated with the metabolic abnormality of diabetes. They include congenital abnormalities, infants who are large for gestational age, and infants who suffer unusual postpartum morbidity and mortality. As discussed earlier, in at least one population, the Pima Indians, NIDDM during pregnancy results in long-term consequences to the offspring, namely increased risk of obesity and of diabetes.

In addition to the characteristic hyperglycemia and other metabolic derangements of carbohydrate and lipid metabolsm, patients with diabetes frequently develop neuropathy and vascular complications. The vascular complications are usually divided into those affecting the small vessels, that is, arterioles and capillaries, and those affecting the large blood vessels, that is the arteries.

Diseases of the small blood vessels associated with diabetes are detectable in the retina and in the kidney, are virtually specific for diabetes, and are strongly related to the duration of diabetes. Diabetic retinopathy may progress to include severe abnormalities such as maculopathy and neovascular changes, which frequently lead to serious visual impairment or blindness. In a survey of patients with known diabetes in Wisconsin, among patients at least 30 years old, the prevalence of retinopathy was 29% within 5 years of the diagnosis of diabetes, 50% within 5-14 years, and 67% in those with at least 15 years of known diabetes (91). The prevalence of proliferative retinopathy was 15% after 15 years of known duration, and it was responsible for 87% of cases of severe visual impairment (visual acuity 20/200 or worse in either eye) in those diagnosed before the age of 30 years. In those diagnosed after the age of 30 years, however, proliferative retinopathy was responsible for only 29% of cases of severe visual impairment. Overall, the prevalence of blindness among diabetic patients was 3.1%.

In the kidney, diabetes often leads to intercapillary glomerulosclerosis, which results in proteinuria, and ultimately to loss of functioning nephrons and to renal failure. About half of those with IDDM develop clinically detectable proteinuria within 30 years of the development of diabetes (92). In Pima Indians with NIDDM, the cumulative incidence of heavy proteinuria was 8% after 10 years, 22% after 15 years, and 48% after 20 years of diabetes (93).

In the larger arteries, diabetes accelerates atherosclerosis, which leads to increased frequency of coronary heart disease and to occlusive changes in the arteries of the lower limbs, which, combined with the increased propensity to infection often leads to gangrene and the need for amputation.

In data from Caucasians in the U.S. National Health Interview Survey, diabetic men reported a history of "heart condition" or "heart attack" 1.6 to 2.5 times as often as non-diabetic men, while diabetic women had corresponding rates of 1.7 to 4.6 times those of non-diabetic women (94). The difference in prevalence rates between diabetic and non-diabetic subjects was greater in those under age 65. After myocardial infarction, the in-hospital survival may be less for diabetic patients (94), and the two-year survival is only about half that of non-diabetic patients (95).

In a community based study in Rochester, Minnesota, peripheral vascular disease, defined by absence of at least one major arterial pulse or presence of gangrene, was more common with increasing age and duration of diabetes (96). The cumulative incidence of peripheral vascular disease was estimated to be 15% at 10 years and 45% at 20 years after the diagnosis of diabetes.

Based on hospital discharge data, 45% of non-traumatic lower extremity amputations in the U.S. are performed on patients with diabetes, who have 15 times the risk of amputation of nondiabetic persons (97).

Mortality

It is not surprising that with all of these serious complications, diabetes is associated with increased mortality. Among life insurance applicants, Goodkin (98) reported that the age-adjusted death rates were

3.35 times as high among people with diabetes as among others. The mortality ratios were inversely related to age at diagnosis of diabetes and were highest (11.3 times nondiabetic rates) for those diagnosed at less than 15 years of age. In the U.S. in 1983, diabetes ranked seventh among certified causes of death, was listed as the underlying cause in approximately 33,000 deaths and as a contributory cause of death in 6.5% of death certificates (99).

Economic Costs

The serious medical complications of diabetes result not only in increased mortality and a great deal of human suffering, but also, of course, in a large economic cost. Two components of the costs of the disease have been estimated. Costs of direct medical care include payments to hospitals, physicians, drugs, and other professional services. Indirect costs include lost earnings due to disability or premature death among people with diabetes. In the U.S. in 1984, the estimated direct costs were 7.4 billion U.S. dollars, and the indirect costs were 6.3 billion dollars, resulting in a total economic burden of 13.7 billion dollars (100). If the cost per patient and the age-specific prevalence rates of diabetes were the same in Canada and the U.S., then the estimated annual cost of diabetes in Canada would be 1.2 billion U.S. dollars. While it would clearly be of value to obtain direct estimates of the prevalence, morbidity, mortality and economic costs of diabetes in Canada, these estimates based on experience in the U.S. and other countries suggest that diabetes may be a problem of tremendous social and economic importance to Canada.

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REVIEW OF EPIDEMIOLOGICAL STUDIES ON DIABETES MELLITUS IN CANADA

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Diabetes can be characterized as a heterogenous group of complex illnesses associated with a disturbance in blood glucose control. It is recognized that the etiology of diabetes is multi-factorial involving both genetic and environmental factors. Diabetes is associated with life-threatening events such as diabetic ketoacidosis and hypoglycemic coma and the development of frequently debilitating long term complications. The psycho-social and economic effects of diabetes on the community are enormous. Research and educational programs have proven that certain types of diabetes can be prevented (primary prevention) (1,2) and complications prevented or delayed (secondary prevention) (3,4,5,6). The marked geographic differences that are identified in the incidence of diabetes mellitus throughout the world would suggest that certain communities are at greater risk for diabetes (7).

Yet, in Canada, little is known about the prevalence and incidence of diabetes, the frequency and severity of complications, the potential etiological factors pertaining to individual communities, nor the the psycho-social and economic impact on the country. The small number of detailed epidemiological studies that have been performed, would suggest that diabetes does represent a major health problem in Canada.

The following studies employed different epidemiological techniques to obtain their data, not all examined type 1 and type 2 diabetes and different criteria were applied for the establishment of the diagnosis of diabetes mellitus.

Prince Edward Island Study

Methods

An epidemiological study in Prince Edward Island has been performed by Tan et al. on information collected between 1966 and 1980 (8,9). Diabetic inhabitants of Prince Edward Island, if registered with the Provincial Department of Health, can obtain urine testing materials and hypoglycemic medications free of charge. This drug program, since 1964, has provided an informal register of diabetic patients living on the Island. Information has been provided on the prevalence and incidence of diabetes, the pattern of drug therapy and an estimate of the cost of providing a diabetes program to the population.

The physician's diagnosis of diabetes was accepted and the criteria of Fajans and Conn were used for diagnostic purposes. Some verification for the correct diagnosis has been made in the latter part of the studies. Both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes (n=2368) were studied and all age groups reviewed. An increase in the prevalence rate from 0.89% in 1966 to 1.9% in 1980 was observed. The majority of patients had the onset of diabetes after the age of 40. The incidence rate of diabetes was 2.12/1000. When age-specific rates are considered, incidence ranges from 0.4-1.41 in patients under 40 and 2.39-10 for those above 40.

An ongoing registry has been established. Further information is being collected on the cost per diabetic patient and the methods of treatment.

Montreal Study

Epidemiological studies into type 1 diabetes have been carried out by Colle and her colleagues (10, 11, 12). Records of 12 hospitals in Montreal, having pediatric wards, were surveyed retrospectively to ascertain the cases of diabetes mellitus from January 1, 1971 to August 1, 1976. Since August 1, 1975 active case finding has been utilized to provide immediate identification of a new case of type 1 diabetes admitted to these hospitals. In the province of Quebec, all children under the age of 15 must be admitted to a pediatric unit thus ascertainment is complete from 0 to 14 years of age. The study was based on patients in the greater Montreal area.

Insulin dependency was defined as patients with hyperglycemia (above 11.1mmol/1(1, 200mg/DL), ketonuria, and a need for insulin. Patients with abnormalities of glucose tolerance tests requiring only diet or diet plus hypoglycemic agents were not included in the study. Only patients with type 1 diabetes (n=588) were entered into the study.

When all patients in the study were considered, an incidence of 8.7/100,000 was established. However, if the groups were divided into those of French Canadian origin and those of other ethnic origin (majority English), there appeared to be minor differences in incidence. The incidence rate for the French Canadian population was 7.4 while for the other ethnic group was 10.4. Incidence was also slightly lower in lower-income groups although these effects were independent of each other. The difference in the socio-economic groups suggested environmental risk factors whereas the difference seen with the ethnic groups, could be due to genetic or environmental factors.

Toronto Study

An incidence study of type 1 diabetes was carried out in Toronto by Ehrlich and colleagues (13). Patients were obtained during a prospective study between 1976 and 1978. In Toronto, all children who develop diabetes are admitted to hospital and this study include only children who reside within the metropolitan area of Toronto. The authors believe that all children who develop diabetes in Toronto were included in the study.

Patients with a typical history of diabetic symptoms and the presence of hyperglycemia and ketonuria were included in the study. Only patients with type 1 diabetes (n=132) were considered. An annual incidence of 9.0/100,000 population under the age of 19 was identified.

Canadian Indian Study

The epidemiologic aspects of diabetes mellitus amongst Indians in northwest Ontario and northeastern Manitoba have been carried out by Young et al. (14). Areas studied included 30 isolated communities in the eastern subarctic area of central Canada. 14,000 Cree and Ojibwa Indians live in this area and are served by the Medical Services Branch of the Department of National Health and Welfare. Cases (n=385) were ascertained by records from the local hospital, records of ambulatory care visits by nurses and physicians, records from peripheral health units and drug dispensing records kept by the zone hospital pharmacy.

The clinical histories of patients identified as having diabetes were reviewed and the biochemical criteria of the National Diabetes Data Group applied to confirm the diagnosis of diabetes mellitus. The patients were not divided into insulin dependents or non-insulin dependent although the type of therapy was recorded.

The overall prevalence rate was 28/1,000. There was a marked predominance of female patients which outnumbered the male 2.5 to 1. The prevalence rate changed from 0.5 in the 0-14 year age group to a high of 125.5 in the 45-64 year age group. Greater than 50% of the patients were treated with oral hypoglycemic agents, 37% with diet alone and 9% with insulin. The authors considered that few of the insulin users could be considered as having true insulin dependent diabetes.

Incidence was not specifically studied but the authors noted that 50% of the cases were diagnosed within the last 5 years of a 25 year period, suggesting that a dramatic increase in incidence has probably occurred.

Health Care Statistics

Further information can be obtained through records kept by Statistics Canada. Examination of standardized death rates from each Province, show widely differing values from 7.8 to 16.8 deaths per 100,000 persons per year. Two national studies have been performed, the Nutrition Canada survey in 1970-72 and the Canada Health Survey in 1978-79. These studies indicated a prevalence of diabetes of 2-2.6%. Very little attempt was made in these studies and surveys, to standardize methodology, types of diabetes, diagnosis and verification.

The majority of the national information is obtained from the records of hospital admissions, health care records and death certificate statistics. It is likely that these figures grossly underestimate diabetes-related events. These discrepancies were clearly identified in a review of the treatment of diabetes in Alberta in 1980 (15). Four Alberta hospitals - 2 urban, 2 rural - were included in a study to ascertain the number of admissions to hospital, where there was a diagnosis of diabetes mellitus. From the hospital discharge records, 1% of all patients were identified as having diabetes. To determine the precise number of diabetic patients within the hospitals, the dietary departments of each of the hospitals were approached, and asked to identify the diabetic patients who were in hospital at that time. It was found that in all the four hospitals reviewed, 10% of all hospital beds were occupied by diabetics at a time when the hospital records indicated only 1% had been admitted with diabetes.

Similar inaccuracies can be identified in death certificates where the secondary diagnosis of diabetes is frequently not even recorded.

Discussion

A summary of the data reviewed in these papers can be seen in Table I. The overall incidence of diabetes in Canada appears to be similar to other studies done in North American communities (7). The data from the four separate epidemiological studies, clearly indicate that genetic, cultural and environmental factors can lead to widely differing prevalence and incidence rates within the overall population. The dramatic differences between the Northern Ontario Indian study and the Toronto, Montreal, Prince Edward Island studies, are an example of the marked ethnic differences within Canada. Registries have been commenced in some areas of the country and will provide some evaluation of population differences at risk for diabetes. There are, however, significant differences in methodology, diagnostic criteria and ascertainment, between the registries described.

Epidemiological data on diabetes within Canada are extremely limited. There is an urgent need to establish clear strategies for ongoing research into epidemiology of diabetes that takes into consideration the multi-ethnic and cultural differences of the Canadian communities.

Table 1

REVIEW OF EPIDEMIOLOGY STUDIES

Studies	Prince Edward Island (1980)			Montreal	Toronto	Ontario
Case Ascertainment	Physicians			Hospital	Hospital	Physicians Health Records
Diabetes Criteria	Fajans and Cohn			Ketosis Insulin Glucose 11.1mm/L	Ketosis Insulin Glucose	NDDG
Age (years)	under 9	10-19	All	under 15	under 18	All
No. of Cases			2368	588	132	385
Type of Diabetes			1 and 2	1	1	1 and 2
Prevalence			1.94%	-	-	All 2.8% 0-14yr. 0.05% 45-64yr 12.5%
Incidence/100,000	40	51	2.12	8.7	9.0	High

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EPIDEMIOLOGIC STUDIES OF TYPE 1 DIABETES MELLITUS

Eleanor Colle, M.D. and J. Siemiatycki, Ph.D.

The studies to be summarised in the following report are those dealing with epidemiological studies of type 1 diabetes mellitus (IDDM). Type 1 diabetes is defined on the basis of the need for insulin to maintain normal metabolic homeostasis and, in the case of children, to support normal growth and development. Virtually all diabetic children less than 16 years of age have type 1 diabetes. A variable number of individuals developing diabetes in the third and fourth decades, and possibly even later in life, may also have type 1 diabetes.

There have been epidemiologic studies reported from all over the world(1-21). Our own studies consist of data gathered from 1971 through 1983 (22). Type 1 diabetics were defined as those children with hyperglycemia (greater than 200 mg/dl),ketonuria, and a requirement for insulin to attain growth and avoid ketoacidosis. The methods used in case finding were as follows: (a) records of the twelve hospitals in the Montreal area having pediatric wards were retrospectively surveyed to ascertain the cases of IDDM from January 1,1971 to August 1,1976; (b) since August 1, 1976 active case finding has allowed immediate identification of each new cases of type 1 IDDM among children aged 0-16 admitted to pediatric wards. The number of hospitals admitting pediatric cases is now reduced and almost all children are admitted to one of three hospitals. In the province of Quebec there is an administrative proscription against admitting children under 15 years of age to adult wards. Thus our ascertainment is probably complete for children 0-14 years of age. However, some diabetics aged 15 and 16 may never have been admitted to a pediatric ward and would not have been ascertained in our system. Therefore the bulk of the results in this report are data on children 0-14 years of age. Incidence was determined as follows: numerators were readily available from our case series data bank. Only cases resident in the Montreal Metropolitan area were eligible. Denominators were derived from tapes of data sent us by Statistics Canada from the censuses of 1971,1976, and 1981. For each of those three years we had numbers of children by age and sex in Montreal. By linear interpolation and extrapolation we estimated the population by age and sex for each year from 1971 to 1983. Not only did the population of children decline across the three censuses from 1971 to 1976 to 1981 but it changed differentially by age group. Thus numbers declined most in the 5-9 age group, somewhat less in the 10-14 and hardly at all in the 0-4. Since incidence of type 1 diabetes varies by age group, time trends in crude incidence rates, except where presented separately by age group, have been standardized to the age distribution of 1971. I shall begin by describing those aspects of the disease which seem to be similar from one study to another.

Age of onset: In study after study the incidence versus age curve is monotonously the same. The incidence rises slowly over the childhood period peaking at the time of puberty. The peak in females always precedes the peak in males by about a year. In most studies there is a slight excess of males in the youngest age group, and this is seen in our data as well. In studies, such as the Danish study (2) where incidence was monitored into the third decade, this adolescent peak was also clearly seen with a decreased incidence in the years following attainment of adult height and weight.

Incidence in males versus females: In all studies, the incidence figures indicate equal numbers of males and females. Amongst the 802 cases in our data there are 394 females and 408 males.

Prevalence of disease amongst first degree relatives: In our study, there were 4% of siblings and 3.5% of parents with type 1 diabetes. (23) This is similar to other studies. Siblings have a 40 fold increase in prevalence of the disease. In a recent study where offspring of patients with type 1 diabetes were ascertained, the incidence amongst offspring of males (6.1%) was higher than amongst female (1.3) diabetics. (24) Thus regardless of the incidence within a geographical area, the prevalence of disease amongst siblings and parents remains constant from group to group.

Association of disease with gene products of the HLA region: We have studied subsets of our total data bank to determine the frequency of HLA-DR alleles.(25) In agreement with all other studies of young diabetics we find that 96% of the children are positive for either HLA-DR3, HLA-DR4, or are heterozygous HLA-DR3/4. The data from the 8th Histocompatibility Workshop suggested that cases of type 1 diabetes in which the onset was in the third decade of life were more apt to express neither of these two high risk antigens. Furthermore, these data suggest that younger children may be more apt to be HLA-DR4 than older children and young adults.

The individual most at risk of developing type 1 diabetes is the identical twin of a diabetic, who has a risk 150 times that of the general population, followed by the HLA identical sibling, who has a risk about 60 times that of the general population. However, even amongst this group the prevalence rate is the major argument suggesting an environmental agent as a necessary additional cause of symptomatic IDDM.

Prevalence of anti-islet cell antibodies: In the 2 years 1976 to 1978 we did a prospective study of anti-islet cell antibodies in newly diagnosed diabetics and their siblings. (26) We found that close to 80% of newly diagnosed diabetics had antibodies against human pancreatic islets at the onset of disease. This also has been found in virtually all studies which have looked at type 1 diabetics at onset of disease.

Thus, taken together these studies show a disease which has an equal incidence in males and in females, which increases in frequency throughout the growing period, which has a strong genetic susceptibility (at least part of which is explained by the association with HLA-DR region products), and which affects a relatively constant, though small percentage of first degree relatives.

I should like next to discuss some areas where there is less agreement between studies.

Overall incidence: The overall incidence in our area is 9.6/100,000 among boys and 9.7/100,000 among girls. There is a considerable variation in overall incidence rates from country to country ranging from a low of 3.7 in France to a high of 26 in Finland. (Table 1). In general, the Scandinavian countries have the highest incidence. These differences could of course be due to differences in study design and case ascertainment, differences in genetic susceptibility, or differences in environmental factors.

Table 1

Population	Study Period	Age range years	Annual incidence per 100000
Finland (12)	1975	14	26
Copenhagen, south (2)	1970-1974	14	20.1
Norway (5)	1973-1977	14	17.6
Scotland (9)	1968-1976	19	13.8
Alleghany County (USA) (16)	1965-1976	20	
White male			16.0
White female			14.8
Black male			10.1
Black female			11.1
Copenhagen, north (2)	1970-1974	14	10.5
New Zealand (7)	1968-1972	20	10.4
Toronto (14)	1976-1978	18	9.0
Montreal (22)	1971-1983	14	9.6
Great Britain (15)	1972-1974	16	7.7
France (6)	1975	14	3.7

Increasing or decreasing incidence: During the 13 year period we found no increase or decrease in incidence. Table 2 shows the numbers of cases and annual incidence rates for type 1 diabetes by age and sex for each year. The data show the yearly incidence rates for each sex group, combining ages, according to the 1971 age distribution. Although there are peaks and troughs, there is no clear evidence of a trend upward or downward. The yearly incidence rates in each age group combining sexes have remained quite stable among the 10-14 year olds and have been most irregular among the 5-9 year olds. The variation in annual numbers of incident cases was statistically significant (p=.003) among 5-9 year olds but not among the other two age groups.

Table 2

Numbers of Cases and Annual incidence rates of IDDM by age and sex from 1971 to 1983, in Montreal

	Age-sex group											
	Boys 0-4		Boys 5-9		Boys 10-14		Girls 0-4		Girls 5-9		Girls 10-14	
Period	**N**	**Inc***	**N**	**Inc**	**N**	**Inc**	**N**	**Inc**	**N**	**Inc**	**N**	**Inc**
1971	5	4.6	17	12.4	18	13.0	11	10.7	14	10.7	16	12.0
1972	6	5.7	12	9.2	17	12.4	3	3.0	16	12.8	14	10.6
1973	9	8.8	11	8.8	22	16.2	5	5.1	16	13.4	15	11.5
1974	3	3.0	6	5.1	11	8.2	6	6.3	11	9.7	12	9.3
1975	9	9.3	14	12.4	16	12.1	4	4.3	20	18.6	21	16.6
1976	4	4.2	8	7.5	15	11.4	3	3.3	11	10.8	17	13.6
1977	2	2.1	7	6.7	20	15.8	9	10.1	10	10.1	15	12.4
1978	6	6.4	13	12.8	13	10.7	6	6.7	13	13.4	13	11.2
1979	2	2.1	5	5.1	16	13.7	3	3.4	10	10.6	16	14.3
1980	4	4.3	13	13.6	14	12.5	6	6.7	6	6.6	12	11.2
1981	4	4.3	10	10.7	16	14.9	3	3.4	13	14.6	7	6.8
1982	9	9.6	5	5.5	15	14.6	3	3.4	-	3.5	6	6.1
1983	11	11.7	9	10.2	11	11.3	7	7.9	6	7.2	12	12.8
1971-76	36	5.9	68	9.3	99	12.2	32	5.5	88	12.6	95	12.2
1977-83	38	5.8	62	9.2	105	13.4	37	5.9	61	9.5	81	10.8
1971-83	74	5.8	130	9.3	204	12.8	69	5.7	149	11.1	176	11.5

* Annual incidence per 100,000.

This lack of trend in incidence over the 13 year period in Montreal agrees with the data from Alleghany County from 1965 to 1976 (16) and that from New Zealand from 1968 to 1972 (7). However, several studies have reported dramatic increases in incidence: in North Sweden (1938-1977) (11), in Scotland (1968-1976) (9), in Glasgow (1933-1976) (18) and in Finland (1970-1979) (12). While the reported increases may be real, they may also reflect improvements in access to medical diagnostic services or record keeping. Alternatively, failure to adjust for changing numbers and shifting age distributions within the population may result in spurious changes in incidence rates. As I have mentioned, this methodologic problem was clear in our data. The population of children declined in Montreal over the time period studied and there was a change in the age distribution with the percentage of children in the highest age group exhibiting the greatest decrease. Failure to adjust rates would have shown a declining incidence rate.

Socio-economic class: In our original survey, we had noted a higher incidence in suburbs with higher socio-economic class (23). However, we realized that we might have a confounding of socio-economic and genetic factors, so we dichotomized our population into two different groups (French-Canadians and non-French-Canadians) and assigned them to one of 5 income quintiles on the basis of census tract of residence at time of diagnosis (8). Statistical adjustments for income and ethnic distributions were made by simple weighing and standard errors computed on the basis of stratification. The results are shown in Table 3. We interpreted the results to show independent ethnic and economic effects. The incidence was significantly higher in the upper sixty percentile of the economic spectrum than in the lower forty; incidence is lower in French Canadians. The lower incidence in the French Canadians is of interest given the low incidence in France which was alluded to above. In both the French and non-French group, however, there was an environmental effect as well. The finding of a higher incidence among the wealthy parallels the prevalence comparison in Israel (27), a small study in Southampton in which Social Class I was overrepresented (28), and an overrepresentation of cases in Social Class I and III in the Barts, Windsor/Middlesex family study (29).

Viral Titers: In our two year prospective study (26), we examined antibody titers against Coxsacki B1-6, rubella, and mumps in the cases at the time of diagnosis and in the sibling nearest in age to the case. Although we found a subset of children in whom there was a rise in titer between the first blood and the second drawn three weeks later (indicative of a recent infection), there was no overall difference in incidence in titers between the cases and their siblings. The subset having evidence of recent infection did not differ from the rest of the cases in regard to age, sex, or HLA typing. Isolation of a variant Coxsackie from an acute case of IDDM has been reported (30) and anecdotal evidence of cases following on antecedent mumps infection are found in the literature. Recently an increase in IgM antibodies to

Table 3
Incidence of Juvenile Onset Insulin Dependent Diabetes in Montreal - By Economic Class and Ethnic Group, 1971-1978

Ethnic group	Income quintile					Total adjusted†
	I	II	III	IV	V	
French Canadian						
Cases	57	49	109	76	51	
Population under 17	122,918	130,791	132,479	114,313	78.776	
Inc/10^5/year+	5.8	4.7	10.3	8.3	8.1	7.4 (6.6-8.2)
Other						
Cases	28	20	28	62	108	
Population under 17	45.356	38.327	38.497	53.567	94.169	
Inc/10^5/year+	7.7	6.5	9.1	14.5	14.3	10.4 (9.3-11.5)
Total adjusted* Inc/10^5/year^1	6.4 (5.0-7.8)	5.4 (4.0-6.8)	10.0 (8.2-11.9)	10.3 (8.6-11.9)	10.2 (8.6-11.8)	8.7 (8.0-9.4)

*Adjusted to common ethnic distribution; 95% confidence limits in parentheses.
†Adjusted to common income distribution; 95% confidence limits in parentheses.
+Incidence per 100,000 children per year.
I to V in increasing level of income.

Coxsackie in newly diagnosed cases has been described (30). The anti-islet cell antibodies have been shown to precede the onset of IDDM by months or years and diabetes following congenital rubella infection may not become symptomatic for up to 20 years following infection. With this in mind those who favor a viral etiology suggest that in addition to causing an acute cytolytic effect the viral infection may alter the immune system of the virus, and act as a "slow-virus". If it is the former, then a number of viruses may play this role and studies designed to focus on only a few may always be doomed to failure. If it is the latter, unless there is a constant latent period between infection and symptoms, epidemiologic studies will also probably fail and a more precise method to document persistent infection in a small group study would be the most economical form of approach.

Seasonality: The data on the percentage of cases with onset in each calender month is given in Table 4. It is seen that there is greater monthly variation among males than among females and slightly more among the younger than the older, the latter being due to smaller sample size. We performed two analyses on this data. A goodness of fit chi square revealed no strong evidence of non-uniformity. Using Roger's test, the excess of cases in August to January was highly significant. Boys showed the pattern more strongly than girls and the high incidence months tended to be contiguous.

Most studies have purported to show some seasonality. In Patterson's study from Scotland (9) there was statistically significant seasonal variation in October/November and January/February in those over 5 years of age. In France (6) a greater incidence was found in October-February, in Norway (5) in October and in February. In Alleghany County (19) there was a decreased number of cases in the summer amongst 5-9 year olds and in the 10-14 year olds was more pronounced in males than in females. A decreased number of cases in the summer was reported in the British (20) study in the group of children greater than 5 years of age. Thus most studies have found an effect of season on frequency of cases especially in those more than 5 years of age and more marked in males than in females. In our study there was a 25% excess of cases in the high risk season (September through February), so that the seasonal effect is a weak one. This is also the case in other series, where the seasonal effect is a weak one and the "season" of high risk often includes all but the summer months. Seasonality has been used as evidence for an infectious component in the etiology of type 1 diabetes. However, an artifactual seasonal effect could be secondary to vacation patterns among cases and among medical workers which could delay care-seeking and/or diagnosis.

Space-time clustering: We sought to examine our cases more closely to see if there was evidence of space-time clustering. Space time clustering is the phenomenon whereby there is a tendency for groups of cases to occur in clusters in the same sub-area in the same sub-period of time. Although there was evidence of time-space clustering in the

Table 4
Percentage of Cases With Onset in Each Calendar Month and Tests of Seasonality, for All Children Aged 0-14 and Sub-groups

		Ages combined		Sexes combined		
	All (n=802)	Boys (n=408)	Girls (n=394)	0-4 (n=143)	5-9 (n=279)	10-14 (n=380)
	%	%	%	%	%	%
January	9.9*	10.0	9.6	7.7	8.6	11.6
February	8.2	6.6	9.9	4.9	10.8	7.6
March	7.7	8.3	7.1	7.7	9.0	6.8
April	7.9	5.9	9.9	7.0	7.5	8.4
May	6.4	5.6	7.1	9.8	5.7	5.5
June	6.4	6.4	6.3	5.6	5.4	7.4
July	8.1	9.6	6.6	8.4	5.7	9.7
August	8.5	8.1	8.9	11.9	8.2	7.4
September	10.2	10.8	9.6	11.2	11.1	9.2
October	8.5	9.3	7.6	7.7	9.3	8.2
November	8.9	8.9	8.6	8.4	9.0	8.7
December	9.5	10.6	8.6	9.8	9.7	9.5
Standard dev. of %-ages	1.2	1.8	1.3	2.1	1.9	1.6
x^2 for goodness-of-fit	15.4	18.0	9.2	8.1	13.5	12.4
P-value from goodness-of-fit	.16	.08	.61	.70	.26	.33
P-value from Roger's test	.01	.00	.27	.25	.02	.16

* Based on the null hypothesis of uniformity, one would expect 8.3% per month. For highlighting purposes, figures of 9.0% and over have been underlined.

years 1971-1973 and a hint of clustering in 1974-1976 there is little else subsequently. Two other clustering analyses did not show evidence of clustering. The conclusions which we drew from these data were that we would have expected to find clear consistent evidence of space-time clustering if and only if all of the following conditions held: (a) most or all of IDDM is caused by a transmissible agent; (b) the agent is neither ubiquitous nor is it so infectious that it sweeps through the entire city in a matter of days; (c) the agent induces IDDM in a fairly short time after infection (perhaps within 6 months), or at least with a very constant latency period between infection and IDDM onset and (d) IDDM is not a very rare sequela of the infection (probably at least 10%). We conclude that at least one, if not more, of the conditions do not hold.

Thus the results of our 13 year population based study confirms the increased incidence of IDDM with age of case with a peak incidence at 11 years in girls and bimodal peaks at ages 5 and 12 in boys, as well as the equal incidence over the 13 year time span when the data are corrected for the changing age distribution of the population at risk. There is a weak evidence of fluctuation in year to year incidence and a weak seasonal effect. There is no consistent space time clustering of new cases.

In recent years it has become apparent that type 1 diabetes is a multifactorial disease. The presence of high risk HLA-DR antigens are markers which identify individuals with a strong genetic susceptibility. Pathologic study of pancreas from recently diagnosed diabetes coupled with evidence of humoral and cell mediated immunoregulatory perturbations and the demonstration of a prolongation of the remission phase by drugs which modulate immune function have strengthened the hypothesis that in some cases, at least, the B cell dysfunction is an autoimmune process. There is evidence that this process may be present for months or even years preceding the onset of clinical symptoms.

At this point we decided to devote our time to setting up case-control studies in which many factors from cases and controls could be examined to generate specific hypotheses. We are midway through the data collection and analysis phase of the case control study. Factors on which we are collecting data are the following: socioeconomic level, educational level, type of housing, crowding within housing, breast feeding, amount of contact with other children at various ages, as well as a variety of objective measures of stress (death in family, job loss, school failure, etc). Analysis of the first 58 pairs shows that there were no differences between cases and controls for the following variables: type of housing, density of housing, history of pets, breast feeding, consumption of selected preserved meats and parental smoking. However, cases differed from controls in some stress related and psychological variables. Since the weak seasonal and yearly variation alluded to above could be related to psychological factors concerned with return to school, change of school, or other school related factors, we think that this is an area in which more data are required.

Future Directions:

1. It appears at the present that the events leading to the islet cell destruction are taking place in a silent period before the onset of symptoms. Therefore intensive study of the only group known to be at high risk, (twins, HLA identical sibling, and offspring of male type 1 diabetics) would seem to be the most productive way to examine such things as (a) correlation of viral infections with evidence of changes in humoral (anti-islet cell antibodies) or cell mediated (T cell subset changes) immunity (b) effect of growth on B cell reserve and (c) effects of psychological changes on immune status. Since each clinic has so few of such children and since the incidence even amongst twins and HLA identical sibs is only 30% over a 10-20 year period, pooling of data from different clinics would seem to be the most economical type of design.

2. Testing for specificity of markers for IDDM should be performed. Although it is clear that most children have antibodies against islet cell antibodies at the time of diagnosis, it is important to determine the prevalence of antibodies in a childhood population and to monitor the course of those children found to be positive.

3. The uniformity of descriptive data from Caucasians in the United States, western Europe, Australia and New Zealand with that from our study suggests that further descriptive data will be confirmatory of that already published. It would be of interest to determine exact incidence figures for the Inuit and the Indian populations. Since the data on correlations between socio-economic class and incidence rates and on correlations between urban and rural area incidence rates are different from one study to another, the collection of such data would be of interest. We would stress that an effort be made to include information about ethnic origin in such data and that the denominators be stratified on this basis as well.

4. Finally we believe that focussed case-control studies may serve to test specific hypotheses.

5. When cohorts of clearly identified type 1 diabetics have been identified, follow-up studies of morbidity and mortality, fertility, and complications should be undertaken.

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SOCIO-ECONOMIC IMPACT OF DIABETES MELLITUS

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Diabetes mellitus is a chronic health problem that affects an estimated one half million Canadians. Because of the chronic nature of diabetes, the diabetic patient represents one of the major users of the health care system. Diabetes will not only have a major impact on the economics of the individual, family and government but also, on the social environment in which the diabetic patient must live.

PSYCHO-SOCIAL IMPACT OF DIABETES

The Diabetic Patient

The diabetic must face many difficult problems related to diabetes. At the beginning, there is the stress of diagnosis and the overall acceptance of a condition that will be with them for life. For many, it represents a change in lifestyle patterns particularly eating, exercise and overall regimentation of routines. They must deal with the threat of chronic complications and perhaps a decrease in the quality of their life due to the development of complications. In an effort to prevent complications, the patient is asked to undertake an almost bewildering number of tasks - eating specific foods, exact meal times, urine testing, finger prick blood tests, insulin injections and adjustment and consistent contact with the health professional team.

The Family Unit

The presence of a diabetic in the family will frequently lead to disruption of usual family routines often causing a focus within the family on particular individuals because of their diabetes. This can often result in sibling rivalry and conflict between parents and patient as to who will take responsibility for daily management. Inevitably, there will be frustration with the mechanics of the health care system.

Marriage

The very decision of marriage may be a complex one as the selected partner has to accept a shared responsibility for the daily management and regimentation of routine. Marital stress can also develop if diabetes is diagnosed after the marriage causing undue strain between the partners. A concern for their offspring developing diabetes may be a major factor in disturbing the marriage.

Pregnancy

The awareness that a well managed diabetic pregnancy can result in a marked reduction in the complications normally associated with the diabetic pregnancy places considerable stress and responsibility on the diabetic mother. There is need for increased regimentation, tests and hospital visits. There is a constant concern about the child having diabetes and possible complications resulting from the diabetic pregnancy. An abnormal pregnancy or outcome will inevitably result in guilt feelings on the part of the diabetic mother.

Career Selection

There are many specific employment restrictions that forbid Type 1 (insulin dependent) diabetics from achieving normal employment goals. These include taxi drivers, bus drivers, heavy equipment operators, aircraft pilots and many other occupations that potentially may result in harm to the general public. Of far greater concern, is the presence of job discrimination for the diabetic because of the belief that the diabetic will have greater health problems than the non-diabetic and may not be able to fulfill their job requirements (1,2,3). Occupations involving frequent shift changes can be restricting and lead to ill health unless dealt with correctly by an education health professional team. The diagnosis of diabetes may also lead to dismissal from the current employment or a change in job status (4).

Insurance

Insurance companies traditionally bar the diabetic from routine insurance policies and impose heavy penalties on even the well controlled diabetic. This specifically applies to professionals requesting disability insurance and is also present in general health insurance policies.

ECONOMIC IMPACT

Medication and Support Costs

There is a bewildering array of materials required by diabetics including urine testing materials, blood testing strips, glucose meters, lancets, swabs and specific diets that frequently require expensive dietary supplements. Table I reviews the yearly costs for an insulin dependent diabetic who may be using home glucose monitoring techniques and indicates that the yearly costs can range from $1000-2200 per year for supplies alone. Reimbursement to the diabetic varies from province to province and some insurance companies will also pay part of the costs involved in the management of diabetes (Table II).

Pregnancy

Because of the need for intensive medical management during the pregnancy, costs to the pregnant mother will rise. There will be need for increased glucose monitoring in the pre-pregnancy stage, increasing insulin dosages and multiple insulin injections requiring more supplies. The pregnant mother will be required to make frequent medical visits to both physician and obstetrician and this may result in forcing her to leave her employment at an earlier date than necessary.

Career Costs

A new diagnosis of diabetes may cause a career change and a loss of lucrative employment choices.

Insurance

Premiums for life insurance and long term disability coverage will add further to the expense of diabetes.

Health Care Costs

The diabetic constitutes one of the most frequent users of the health care system involving visits to office, hospital outpatient and hospitalization (5,6,8). Minimal data are available in Canada as to the extent of these costs but adjusting figures available from the United States to the Canadian population, it is clear that costs are high. Almost three percent (2.82%) of visits (1.7 million) to the physicians office involved a diagnosis of diabetes (7). In the United States, diabetes was listed as one of seven discharge diagnoses for 2.25 million hospitalizations where people with diabetes were 2.3 times more likely to be hospitalized than age matched people without diabetes in the general population. Based on the U.S. data, the total direct cost of diabetes in Canada can be estimated to be 0.79 billion dollars per year. When indirect costs are considered, such as person-years lost from work each year by people employed with diabetes, and the number of years of life lost each year to diabetes, the indirect costs can be estimated to be in the vicinity of 1.0 billion dollars per year (9,10).

Recent data from the province of Alberta would indicate that these costs may be underestimated. Reviewing government statistics, diabetes mellitus was the primary diagnosis for 3,819 of all hospital discharges in 1977, representing 1% of all discharges. When an intensive review of hospital admissions was undertaken in selected hospitals, however, it was clear that diabetes mellitus represented 10% of primary diagnoses for hospital admissions. Also, as in the United States, the hospital stay was substantially longer than for the average non-diabetic patient.

It is clear from this brief review of these data, that diabetes mellitus has a major socio-economic impact on the community. There is an urgent need to establish Canadian data and to develop strategies to overcome these serious problems.

Table 1
Costs Incurred Per Year For Diabetes Management

		Number of Daily Injections			
		1	2	3	4
1)	Syringes $19.00/100	$ 68.35	$138.70	$208.05	$277.40
2)	Insulin (40U per day)				
	- beef/pork - $11.00/vial		$160.00		
	- pork - 14.00/vial		204.40		
	- human - 16.00/vial		233.60		
3)	Urine testing $9.00/100	$ 40.15	$ 80.30	$120.45	$160.60
4)	Testing Strips $16.00/25	233.60	467.20	700.80	934.40
5)	Alcohol swabs $4.50/100	16.43	29.20	43.80	58.40
6)	Lancets $12.00/200 - re-used 5 times	4.38	8.76	13.14	17.52
7)	Monojector $8.00				
8)	Meter - $200.00				
9)	Dietary Supplement Average $30.00/month - $360.00/year				
	Total for one year				
	Beef/Pork	$1091.90	$1452.16	$1814.24	$2176.32
	Pork	1136.30	1496.56	1858.64	2220.72
	Humulin	1165.50	1525.76	1887.84	2249.92

Meter Costs of $200.00 will be deducted on subsequent years.

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DIRECTIONS FOR THE EPIDEMIOLOGY OF DIABETES IN CANADA

Donald T. Wigle, M.D.

Introduction

The disease surveillance program within Health and Welfare Canada has not included diabetes. Our current chronic disease epidemiology program includes cancer, cardiovascular disease, birth defects and accidents. With a total staff of 18 persons and an operating budget of less than $100,000.00 per year, it is a challenge to do worthwhile work in these four major disease areas. Despite a lack of expertise in the diabetes field, I have tried to apply my experience in chronic disease epidemiology to the subject of this Task Force.

Ideal Situation

Epidemiology has been defined as "the study of the distribution and determinants of health-related states and events in populations and the application of this study to control of health problems"[1]. In the present context, epidemiology should provide information on the extent of diabetes in the Canadian population and the underlying causes and aggravating or protective factors. In addition, epidemiologic methods should be used to evaluate early detection tests (for sensitivity and specificity) and treatment regimens (for efficacy over the short and long term). This information, when available, should be used to develop or improve primary, secondary and tertiary prevention programs aimed at reducing the burden of sickness, disability and premature deaths caused by diabetes. Definitions of these types of prevention programs are as follows:

TYPES OF PREVENTION PROGRAMS

PRIMARY PREVENTION CAN BE DEFINED AS THE PROMOTION OF HEALTH BY PERSONAL AND COMMUNITY-WIDE EFFORTS, E.G., IMPROVING NUTRITIONAL STATUS, PHYSICAL FITNESS, AND EMOTIONAL WELL-BEING, IMMUNIZING AGAINST INFECTIOUS DISEASES, AND MAKING THE ENVIRONMENT SAFE.

SECONDARY PREVENTION CAN BE DEFINED AS THE MEASURES AVAILABLE TO INDIVIDUALS AND POPULATIONS FOR THE EARLY DETECTION AND PROMPT AND EFFECTIVE INTERVENTION TO CORRECT DEPARTURES FROM GOOD HEALTH.

TERTIARY PREVENTION CONSISTS OF MEASURES AVAILABLE TO REDUCE IMPAIRMENTS AND DISABILITIES, MINIMIZE SUFFERING CAUSED BY EXISTING DEPARTURES FROM GOOD HEALTH, AND TO PROMOTE THE PATIENT'S ADJUSTMENT TO IRREMEDIABLE CONDITIONS. THIS EXTENDS THE CONCEPT OF PREVENTION INTO THE FIELD OF REHABILITATION.

The type of epidemiologic study required depends on the objective. Primary prevention requires knowledge of underlying risk or protective factors which can be controlled to reduce the risk of developing disease. Epidemiologic approaches capable of identifying risk factors include case-control, cohort (follow-up) and intervention studies. Secondary prevention requires early detection and treatment to minimize disability and risk of premature death once the disease has developed. Epidemiologic evaluation of methods for early diagnosis involves calculation of the sensitivity and specificity of screening procedures. Evaluation of treatment regimens or combined screening/treatment regimens is best done through randomized trials. Factors involved in progression of disease can be identified through case-control or cohort studies. Treatment or other regimens aimed at slowing disease progression are best assessed through randomized trials.

Reasonably accurate measures of the incidence and prevalence of diabetes in the population would permit the following: i) rational planning of health and social services for diabetics; ii) identification of significant changes in risk over time and differences in risk between population subgroups defined by ethnicity, sex, age, socioeconomic status and geographic region. The latter data are useful for "targetting" research and health care programs and are essential to assessment of progress. Follow-up of cases newly diagnosed within defined populations (e.g. a province) would permit determination of disease complication and survival rates and assessment of quality of life indicators.

Actual Situation

The little epidemiologic research of diabetes that has been done in Canada is reviewed elsewhere in this volume by Dr. Stuart A. Ross. There are limited data on the extent of diabetes in Canada. Examples of mortality data are given in Tables 1 and 2.

Table 1
Age-Standardized Diabetes Death Rates
Canada, 1951-53 TO 1981-83

MALES	0-24	25-54	55-74	25-74	75+	ALL AGES
1951-53	0.9	4.4	34.2	12.3	102.5	9.5
1961-63	0.3	4.3	39.4	13.6	146.1	11.2
1971-73	0.2	4.5	47.2	15.9	206.7	14.0
1981-83	0.1	3.1	34.5	11.5	168.7	10.7
% CHANGE (1971-73 TO 1981-83)	-50	-31	-27	-28	-18	-24
FEMALES						
1951-53	0.9	3.9	60.3	18.9	135.3	13.7
1961-63	0.5	3.1	57.9	17.7	169.1	14.0
1971-73	0.2	3.0	50.3	15.6	209.9	14.0
1981-83	0.1	2.1	29.7	9.4	164.5	9.6
% CHANGE (1971-73 TO 1981-83)	-50	-30	-41	-40	-22	-31

DEATHS PER 100,000 PERSONS PER YEAR

Table 2
Age-Standardized Diabetes Death Rates (Age 25-74)
By Province, 1981-83

	Men	Women
NEWFOUNDLAND	9.3	11.6
P.E.I.	9.9	8.1
NOVA SCOTIA	16.8	13.2
NEW BRUNSWICK	12.5	11.6
QUEBEC	13.5	11.0
ONTARIO	11.5	9.2
MANITOBA	11.9	8.2
SASKATCHEWAN	10.5	9.3
ALBERTA	8.7	7.5
BRITISH COLUMBIA	7.8	6.8

The age-standardized diabetes death rate (all ages combined) increased from 9.5 to 14.0 among men between 1951-53 and 1971-73 (Table 1). The rate for women was relatively constant at about 14 throughout this period. Both rates declined by 1981-83 but more rapidly for women so that the rate was then lower among women (in contrast to 1951-53 when the death rate was 44% higher among women compared to men). Death rates declined among men and women in all age groups between 1971-73 and 1981-83.

The diabetes death rates varied by province (Table 2). The highest rates (Nova Scotia) were about double the lowest rates (Albert, British Columbia).

Diabetes was responsible for 1% of potential years of life lost prior to age 75 in Canada during 1983 (Table 3).

Table 3
Potential Years Of Life Lost Before Age 75
Canada, 1983

	Men	Women	Total
DIABETES	9,120	7,912	17,032
ALL CAUSES	1,142,570	613,363	1,755,933
% DUE TO DIABETES	0.8	1.3	1.0

The prevalence of diabetes can be estimated by survey. Small surveys conducted in three Canadian communities about 1950 revealed abnormal glucose tolerance tests among 1% of males and 1.4 to 1.6% of females age 5 or older[2,3]. Recently, a study of diabetes among Indians in northwestern Ontario and northeastern Manitoba was reported[4]. The authors used hospital, ambulatory health care and drug records and biochemical criteria of the National Diabetes Data Group to confirm diabetic cases. The prevalence rates were 4.6% for age 15-64 and 9.6 % for age 65 or older. Risk factors for complications of diabetes were duration of diabetes and hypertension.

Two national surveys have included measures of diabetes, the Nutrition Canada Survey (1970-72) and the Canada Health Survey (1978-79). Neither survey included a glucose tolerance test. Self-reporting of diabetes and use of drugs for diabetes were recorded. The data are summarized in Table 4.

Table 4
National Survey Data On Diabetes

	Men	Women
Nutrition Canada Survey (1970-72)		
- Percent Currently Treated	1.9	1.7
- Percent Ever Treated	2.6	2.7
	(Age 20+)	
Canada Health Survey (1978-79)		
- Percent Reporting Diabetes	1.7	2.5
	(Age 15+)	
- Percent currently Using Drugs For Diabetes	0.5	0.9
	(All Ages)	
- Percent Fasting Blood Glucose 160 MG/DL	1.2 (Both Sexes, All Ages)	

The prevalence of diabetes was about 2.6% in the Nutrition Canada Survey (age 20+) and 2% in the Canada Health Survey (age 5+). The prevalence of blood glucose of at least 160 mg/dl after fasting for at least 1½ hours was 1.2% in the Canada Health Survey (both sexes, all ages.)

Health care utilization, disability, family history and smoking habit of diabetics and non-diabetics age 35-64 in the Canada Health Survey are presented in Table 5.

Table 5
Comparison Of Diabetics And Non-Diabetics (Age 35-64)
Canada Health Survey, 1978-79

	Diabetics	**Non-Diabetics**
Consulted Physician 3 or More Times In Past Year	76%	35
Hospitalized During Past Year	15	10
Major Activity Limitation	37	14
Average Disability Days (Last 2 Weeks)	2.1	0.8
Use Of Drugs For Diabetes	43	0
Father Diabetic	18	7
Mother Diabetic	29	12
Regular Cigarette Smoker	31	42

The data reveal that diabetics experienced considerably higher health care needs and disability compared to non-diabetics. Family history of diabetes was about 2½ times as frequent among diabetics. The prevalence of cigarette smoking was lower among diabetics but was still considerable (31%).

Hospitalization data for diabetes are presented in Table 6.

Table 6
Hospitalizations For Diabetes
Canada, 1980-81 (Fiscal Year)

	Males	**Females**	**Total**
Admissions	18,060	22,644	40,704
Hospital Days	335,916	452,880	788,796
% Of Total Hospital Days	1.8	1.9	1.8

Diabetes was the discharge diagnosis for 40,704 hospital admission/separations and accounted for almost 2% of all hospital days.

Conclusions

The data reported here indicate that diabetes is a major health problem in Canada. However, the data are incomplete and the true size of the burden of illness, disability and premature death due to diabetes must be very large. Mortality rates declined among all age groups during the period 1971-73 to 1981-83. The absence of incidence and/or survival data means that it is not possible to determine the reason(s) for this recent mortality rate decline. Possible reasons (apart from artifacts) include one or more of reduced risk of developing diabetes, reduced severity of disease and improved treatment.

Recommendations

1. The National Diabetes Task Force should obtain sustaining funds so that a national program to combat diabetes can be developed and implemented.

2. The national program should include:
   (a) periodic national surveys to determine the prevalence of diabetes in Canada.
   (b) follow-up of subjects included in national surveys to permit estimation of diabetes incidence, complications and survival rates (computerized record linkage procedures should be used to reduce the cost of follow-up).
   (c) registration and follow-up of all diabetics within defined populations (e.g. city or province) - to permit assessment of complication and survival rates in relation to treatment history.
   (d) case-control studies of newly diagnosed cases to assess the importance of potential causal or protective factors.
   (e) "case-control" studies of complicated cases and uncomplicated diabetic controls to assess the role of factors which may accelerate or retard the progression of diabetes.

3. A national program should be initiated to reduce the prevalence of smoking among diabetics to less than 10% by 1995.

Acknowledgements

I thank Dr. Helen Johansen, Mr. Bill Bradley, Ms. Prem Khosla and Mrs. Anne Lange for their assistance.

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COMPLICATIONS

COMPLICATIONS OF DIABETES
SUMMARY AND RECOMMENDATIONS

Introduction

Despite current methods of treatment the long term microvascular and macrovascular complications of diabetes mellitus occur with alarming frequency and lead to major disability and mortality in otherwise healthy individuals. Although it is clear that the prevalence of these complications increases with increased duration of diabetes, the etiology and pathogenesis are poorly understood. Evidence has been accumulating of a relationship between both genetic factors and the diverse metabolic abnormalities and the development of diabetic complications. However, to date, prospective randomized controlled studies with newer forms of diabetes therapy designed to attain near normal blood glucose control (e.g. insulin pumps and intensified insulin therapy) have failed to demonstrate conclusively prevention or reversal of these complications.

The aim of the following report is to discuss in detail the evidence relating to the role of hyperglycemia in the development of diabetes complications. In addition each of the major diabetes complications has been reviewed comprehensively and specific recommendations relating to detection, management and future research are presented. The current status in Canada and future needs are addressed where possible.

RETINOPATHY

Summary

The best study examining the epidemiology of diabetic retinopathy and its associated risk factors was performed in Southern Wisconsin by Klein and colleagues. The results of this well-controlled study are reviewed in detail in the accompanying manuscript. Although data on a similar Canadian population are not available the results of the Wisconsin study may be extrapolated to similar Canadian populations. Specific areas of interest include the following:

1. Detection of Retinopathy in Canada.

    - A common problem expressed by retinal specialists is that diabetic patients are too frequently referred with advanced retinopathy.
    - There is clearly a general lack of expertise among health professionals in the detection and management of diabetic retinopathy.

2. Intervention Strategies.

   - The results of the Diabetic Retinopathy Study (DRS) have provided excellent absolute indicators for treatment (laser photocoagulation) of high risk eyes. This treatment is unquestionally beneficial.

   - Despite effective therapy, 10% of retinopathy still progresses. This group is presently being evaluated by the Diabetic Retinopathy Vitrectomy Study (DRVS).

   - The timing of treatment of patients without high risk characteristics, such as severe preproliferative retinopathy, is being determined by the on-going Early Treatment Diabetic Retinopathy Study (ETDRS).

   - Macular edema, a very common cause of visual deterioration, has not been proven to be treated effectively by focal laser treatment. Again this issue is being addressed by the ETDRS as well as a proposed Diabetic Macular Edema Study (DMES) which will also examine the role of different wavelengths of laser photocoagulation.

3. Prevention

   - Animal and clinical studies support a relationship between glycemic control and the presence of diabetic retinopathy. However, a cause and effect relationship has not been proven. The United States National Institute of Health sponsored Diabetes Control and Complications Trial (DCCT) should provide a more definitive answer. Until this trial is concluded one must continue to stress the importance of achieving the best possible diabetes control that can safely be achieved with current treatment regimens.

Recommendations

1. Patients should be educated about the need for eye evaluation and treatment.

2. All type 2 diabetics should have an eye examination (by an ophthalmologist) at diagnosis.

3. All type 1 diabetics should have an eye examination by an ophthalmologist within 5 years of diagnosis.

4. All diabetics should be reexamined by an ophthalmologist annually.

5. Education should be organized for general ophthalmologists, internists, endocrinologists, etc. on the importance of early referral and treatment of diabetic retinopathy.

6. Dissemination of new information (ie. symposia to all health professionals should be organized.

7. More retinal specialists interested in diabetes care should be recruited.

8. Research should be stimulated in:
   a) basic science relating to the pathophysiology of diabetes eye disease.
   b) clinical research to evaluate newer treatment modalities.

9. Interested ophthalmologists should be identified and regional centres for treatment should be established.

10. Screening programs for diabetics who do not have access to ophthalmologist services should be developed. (e.g. possibly transporting nurse practitioners trained in eye examination to outlying areas).

DIABETIC NEPHROPATHY

Summary

Progressive diabetic nephropathy ie. glomerulosclerosis, leads to renal failure in 40% of insulin-dependent diabetic patients. Improved glucose control has not been shown to retard the evolution of end-stage renal failure due to diabetic glomerulosclerosis. In the earlier stages, glucose control may reverse, stabilize or prevent diabetic nephropathy. Persistant elevation of microalbuminuria (greater than 30 ug/min) is now recognized as a marker for progressive diabetic nephropathy. Standard methods for determining microquantities of albumin in the urine have not yet been established in Canada. Hence, the sub-group of diabetic patients who might benefit from improved glucose control are not being identified. The reversibility of early progressive diabetic nephropathy is not being investigated in Canada.

A recent survey of Canadian dialysis and transplantation units shows that not all diabetic patients with advanced nephropathy are referred early enough to the nephrologist for optimal management (eg. early renal transplantation). Expert management of advanced diabetic nephropathy should include normalization of blood pressure to help delay the rate of progression. As well, the patient should be informed about the inevitable progression of the disease to facilitate planning for early dialysis and preferably living-related donor renal transplantation.

Recommendations

1. Close attention should be directed to the management of hypertension in all diabetics.

2. Research studies to evaluate the usefulness of microalbuminuria as a marker of early progressive diabetic nephropathy should be initiated and the possible reversibility of this marker with glucose control should be documented in Canada.

3. Once advanced diabetic nephropathy develops (ie. urine protein greater than 300 mg/day, and/or a rise in serum creatinine) the nephrologist should begin to follow the patient along with the endocrinologist or internist. Optimal management of advanced disease should include:
   (a) effective blood pressure control
   (b) early dialysis and transplantation

4. The divisions of nephrology across Canada take a more active role in establishing multidisciplinary clinical settings (including an endocrinologist, nephrologist, ophthalmologist, nurse clinican, dietition, social worker etc.) for the ongoing treatment and clinical investigation of patients with diabetic nephropathy.

5. Canadian scientists should be encouraged to investigate the pathophysiologic mechanisms of diabetic glomerulosclerosis.

DIABETIC NEUROPATHY

Summary

The prevalence of neuropathy is very high in the diabetic population. Approximately 200,000 diabetics in Canada have clinical neuropathy. Of these, about 10,000 have severe disorders with intractable pain, weakness, and/or highly significant autonomic dysfunction. The following points identify some major concerns:

- We cannot yet identify those diabetics who will develop severe neuropathy.
- We do not fully understand the mechanisms underlying the development of neuropathy in diabetics, or the differing clinical expressions of neuropathy.
- As a result, effective therapy is limited, although it is believed that early diagnosis is essential for most effective treatment.

Recommendations

1. Every diabetic should have a neurological examination as part of an annual review with the primary care physician.

2. Patient education concerning the existence of diabetic neuropathy with a simple outline of symptoms and signs should be presented in a pamphlet.

3. Develop quantitative methods of assessment (eg. computerized electrophysiological tests, quantitative sensory threshold determinations, autonomic function tests) to give objective measures which might be followed to assess responses to therapy more accurately.

4. Further research into the pathophysiology (metabolic disturbances, ischemia) is necessary to allow the development of rationale modes of therapy.

5. Different modes of therapy must be tested rigorously. These include modalities such as: prevention of complications by improved diabetes control and the use of drugs (eg. aldose reductase inhibitors), for metabolic intervention.

DIABETES AND MACROVASCULAR DISEASE

Summary

The recommendations with respect to macrovascular disease, the most common complication of diabetes, will be confined to prevention rather than including the treatment of ischemic end organ sequelae since the latter is similar in both diabetics and non-diabetics.

There is much information about risk factors and preventive measures for arteriosclerosis. However, there is little information specifically relating to diabetes. The pathology of atherosclerosis in the diabetic appears to be the same as in the non-diabetic. Hence it is reasonable to examine in the diabetic those atherogenic factors found in the non-diabetic. Specifically some important questions can be identified:

1. Are morbidity and mortality patterns changing in diabetics as in non-diabetics?

2. How much of the diabetic's risk can be attributed to general atherosclerotic factors and how much may be unique to the diabetic (eg. hyperinsulinemia, glycosylation of proteins, etc.)?

3. What is the impact on different types of diabetes of different treatment modalities (insulin, oral hypoglycemics, exercise and diet), sex, age, race etc.?

Recommendations

1. Accurate, specific and sensitive non-invasive methods to assess macrovascular disease. This is not only important to diagnose the disease, but is essential for any epidemiologic studies and assessment of impact of preventive and treatment resources.

2. New advances in lipoprotein classification and apolipoprotein assays should be recognized to examine a) their impact on atherosclerosis and b) the impact of diabetes on lipoproteins.

3. The metabolism of lipoproteins in diabetics should be explored in order to a) determine what metabolic factors result in increased lipoprotein risk effects; b) anticipate intervention strategies to reverse these risk effects; and c) develop methods to "control" diabetes that also address the other atherogenic factors.

4. The relationship of hyperinsulinemia to atherogenesis should be explored further.
   - Does exogenous insulin administration result in hyperinsulinemia that poses an atherogenic risk?
   - Do the route, timing and type of insulin have an impact on the development of atherosclerosis?

5. The changes in platelet function that are a consequence of diabetes (and not associated atherosclerosis) should be examined. It should also be determined which of these may be influenced by diabetes control and develop strategies to diminish any platelet associated risk.

6. Aggressive and effective antihypertensive therapy in diabetic subjects should be developed and implemented.

7. Aggressive anti-smoking strategies should be developed and implemented.

8. In addition to anti-atherogenic strategies in general, effective foot care measures that will prevent injury to diabetics, particularly to ischemic, limbs, should be implemented.

Overall Recommendations

1. Guidelines for the prevention, detection and management of diabetes related long term complications should be developed.

2. The need for regionalization of treatment facitilies in order to implement efficiently the recommended services to both rural and urban diabetic populations should be assessed.

3. The manpower requirements to achieve an acceptable standard of diabetes treatment should be assessed.

4. We should standardize patient and professional information on prevention and treatment of complications.

THE ROLE OF HYPERGLYCEMIA IN THE DEVELOPMENT OF DIABETES COMPLICATIONS

Philip Raskin, M.D.

Introduction

Over the past many years the relationship between the microvascular complications of diabetes and diabetes control has been unclear. There has been an accumulation of considerable evidence that, at least in the experimental diabetes of animals, there is some relationship between antecedent diabetic control and the subsequent development of a characteristic diabetic lesion in their eyes and kidneys. In human beings, this relationship is far from clear. There is evidence on both sides of this issue, and one is unable to come to a firm conclusion regarding the matter because until recently it was next to impossible to provide treatment strategies that would result in normal or near normal blood glucose levels for sustained periods of time in most patients with insulin dependent diabetes. Thus, it was impossible to compare diabetic complications in large groups of patients with normal or near normal blood glucose levels with those in whom blood glucose levels were elevated. The recent development of more effective treatment modalities as well as the rapidly expanding use of self monitoring of blood glucose levels has now made it possible to achieve near-normal glycemia for prolonged periods of time.

It is the purpose of this manuscript to review this issue in considerable detail. I plan to cover the more pertinent older data and to discuss the most recently acquired information in this area, much of which has been accumulated in a prospective fashion.

The Natural History of Diabetes

Table 1 shows the results of two long term studies of the occurrence of vascular complications in patients who have had diabetes for more than 40 years. The incidence of complications in this group of patients is quite low. These patients, who have survived diabetes for more than forty years, may represent a special subset of patients who are different from those we usually see.

There are other data to suggest that the incidence of the various complications rate is higher than these two long-term studies. Figure 1 shows the data of Palmberg. These data are perhaps the best available in two regards. First and very importantly, they show the increased ascertainment of diabetic retinopathy when fundus photography and/or angiography is used rather than just the ophthalmoscope. They also show that 80-90% of patients after 20 years of diabetes have some form of retinopathy.

Table 1
Vascular Complications In Diabetes After 40 Years (1,2)

	Boston	London
Patients	73 (31M, 41F)	92 (32M, 60F)
Therapy	Insulin	Insulin
Complications (%)		
Retinopathy	75.3	60.8
Nonproliferative Type	45.0	43.4
Proliferative Type	17.8	10.8
Proliferative Type (Blind)	12.3	6.5
Nephropathy	41.0	8.6
Proteinuria only	28.7	6.5
Proteinuria and renal failure	8.2	2.1
Neuropathy	48.0	16.3
Ischemic heart disease	20.5	45.6
Peripheral vascular disease	40.0	44.5

With respect to nephropathy, the data of Kussman et al are of interest. They are the result of a retrospective analysis of 112 type 1 diabetic patients listed in the death registry of the Joslin Clinic between 1962 and 1972 as well as patients diagnosed as having diabetic nephropathy from 1966-1967. It is evident that nephropathy was far more common and more severe in this group of patients than in those patients in the forty year studies.

Table 2
The Development Of Nephropathy In Type 1 Diabetes Mellitus (27)

			Mortality		
No.	**Duration of Diabetes Onset of Proteinuria**	**Time Onset of Proteinuria to Renal Failure**	**Overall**	**Renal Failure**	**Cardio-vascular Disease**
Patients	(years)	(years)	%		
112	17.3 ± 6	4.0	53	59	36

Figure 1

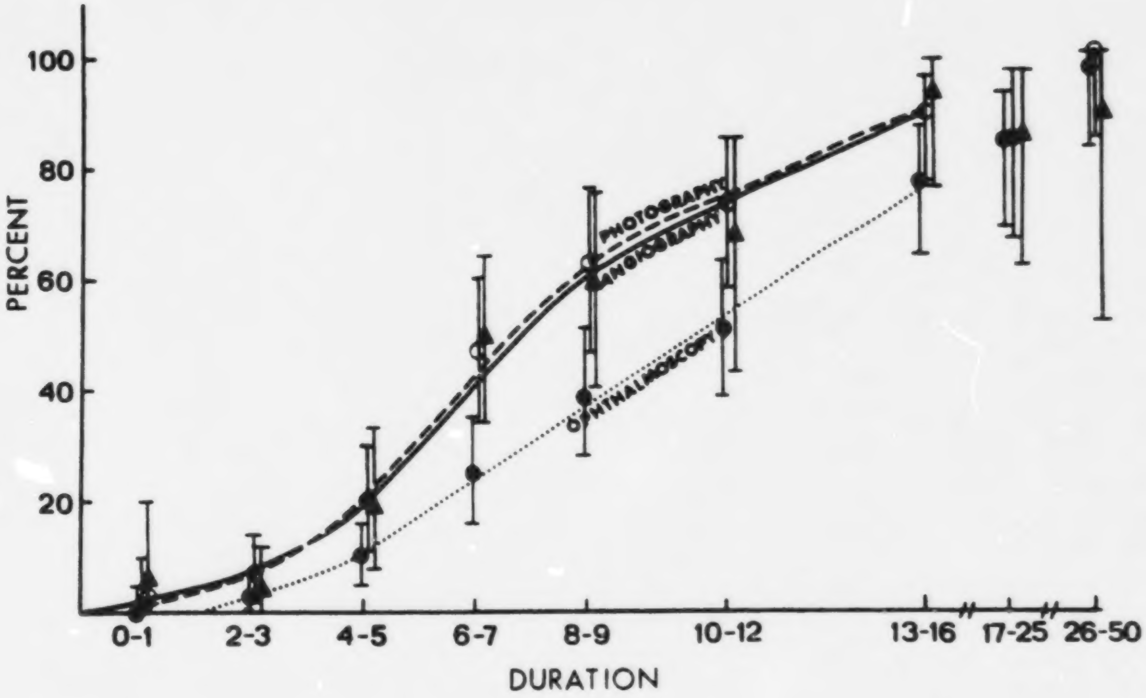


Figure 1. Prevalence of retinopathy. The prevalence of retinopathy is given for the modalities of (closed circle) opthalmoscopy, (open circle) photography, (closed triangle) fluorescein angiography, at each duration of disease (43).

What is important to note from all of this, and an issue that I will return to, is that there is a group of patients with typical insulin dependent diabetes mellitus, who despite many years of diabetes, never get the severe complications of the disease. This fortunate subset of patients makes up approximately 20-25% of patients. Also of interest is the fact that there is an even smaller group of patients, perhaps 5% of patients who get severe complications of diabetes in the face of only mild elevation of blood glucose and a short duration of diabetes. These are the unfortunate people whose first indication that they have diabetes is when they seek medical attention because of one of the small blood vessel complications of diabetes.

Because there are such widespread differences in the appearance of diabetic complications in patients there have been two major hypotheses advanced regarding their pathogenesis. The first of these, the genetic hypothesis, suggests that the small blood vessel complications of diabetes are in no way related to the metabolic abnormalities of diabetes, but are in some way genetically predetermined as part of the diabetic syndrome. Thus, people with diabetes get diabetic complications because they are in some way genetically predisposed to do so. The other hypothesis, the metabolic hypothesis, suggests that the development of diabetic complications is a direct consequence of the hyperglycemia of diabetes. If one could prevent the hyperglycemia of diabetes, then one would not develop diabetic complications. Arguments between the proponents of these two seemingly opposite hypotheses are legion.

Diabetic Complications: Genetic Influences

The strongest piece of evidence against the hypothesis that diabetic microangiopathy is the consequence of the metabolic abnormalities of the disease and in support of the genetic hypothesis has come from our Department. Siperstein et al, using a simple morphometric method for measuring the basement membrane thickness of quadriceps muscle capillaries clearly showed (Table 3) that greater than 90% of adults (19 years of age and over) with diabetes had an abnormal capillary basement membrane thickness as compared to a group of normoglycemic controls with a negative family history of diabetes (59).

Table 3
Quadricep Capillary Basement Membrane Width
In Normal, Diabetic And Prediabetic Subjects (59)

Subjects	**Average Basement Membrane Width (A)**	**Prevalence of Basement Membrane Thickening %**
Normal (50)	1080 + 27	8
Diabetic (51)	2403 + 119	98
Prediabetic (30)	1373 + 44	53

In addition, he showed that of 30 genetic prediabetic (offspring) of two overt diabetes) adults, whose glucose tolerance was normal, 53% had thickened capillary basement membranes as compared to the control group. In these studies there was no correlation between the severity or duration of the diabetes and the thickness of the basement membrane. Mean capillary basement membrane thickness in 29 "mild" diabetics treated with diet and/or tolbutamide was 2410 + 167 A° whereas in 22 "severe" diabetics requiring insulin therapy it was 2395 + 173 A°. There was also no differences seen in basement membrane thickness when the patients were divided into those whose disease began before or after age 21. There was also no correlation between the width of the basement membrane and the duration of the disease. Lastly, he showed in 8 patients with "secondary" diabetes due to chronic pancreatitis, some of whom had long standing fasting hyperglycemia, that only one patient (20%) had a thickened basement membrane.

These data have been criticized over the years for many reasons and I wish not to spend any time on this controversy. Suffice to say, although there has been considerable disagreement over the precise prevalence of the lesion of a thickened skeletal muscle capillary basement membrane in human diabetes as well as its relationship to the age of the subject or to the duration of the diabetics, yet a thickened basement membrane in skeletal muscle capillaries from diabetic patients is a finding confirmed on many occasions.

Finally, more evidence with respect to a genetic factor being operative in the development of diabetic microvascular disease was provided by Marks, et al (31). They measured skeletal muscle capillary basement membrane thickness in 38 unaffected parents (i.e. with normal oral glucose tolerance tests) of children with insulin dependent diabetes mellitus and found a striking relationship between the presence of the antigen HLA-DR4 and the thickness of the skeletal muscle capillary basement membrane.

Table 4
Correlation Between Basement Membrane Thickness (BMT)
And HLA-DR4 (31)

HLA Phenotype of Parents	**Mean BMT (A°)**	**Number**	
		BMT 2000	**BMT 2000**
HLA-DR4 Positive	2026 + 350*	12	8**
HLA-DR4 Negative	1642 + 373	2	6
Normal Subjects	1628 + 218	8	10

*p .001, t-test (DR4 pos. vs. neg.)
**p .005, fisher test (DR4 pos. vs. neg.)

Dornan et al, in a very interesting study, compared the incidence of retinopathy in a group of 127 insulin-dependent diabetic patients in relationship to the HLA haplotype (12). Interestingly, they found that HLA-DR4 was present in 70% of patients with background or proliferative retinopathy and in only 54% with no retinopathy. They also found the retinopathy tended to be more common in patients with "poor diabetic control" (Figure 2). The combination of poor diabetic control and HLA-DR4 increased the odds of having retinopathy to 33.3%. They concluded that genetically determined factors appear to influence susceptibility to retinopathy. This relationship between HLA-DR4 and a seemingly increased susceptibility to retinopathy has not been confirmed by other investigators.

Diabetic Complications: Metabolic Influences

When one discusses the metabolic influences on the development of diabetic microvascular disease one should consider the answer to the following important questions:

The Important Questions

If we control hyperglycemia in diabetes, can we:

1. Prevent the development of diabetic complications?
2. Reverse established diabetic complications?
3. Slow the progression of established diabetic complications?

Studies using immunohistochemical techniques have added considerable information with regard to renal lesions in diabetes. Miller and Michael carried out a comprehensive immunofluorescent analysis on renal tissue from three groups of patients (39). One group consisted of 24 living normal renal allograft donors and two infants less than one week of age (Group I). Group II included 24 patients with severe nephropathy, who had diabetes mellitus for 16 to 30 years duration. Their ages ranged from 20 to 47 years. The last group (Group

Figure 2

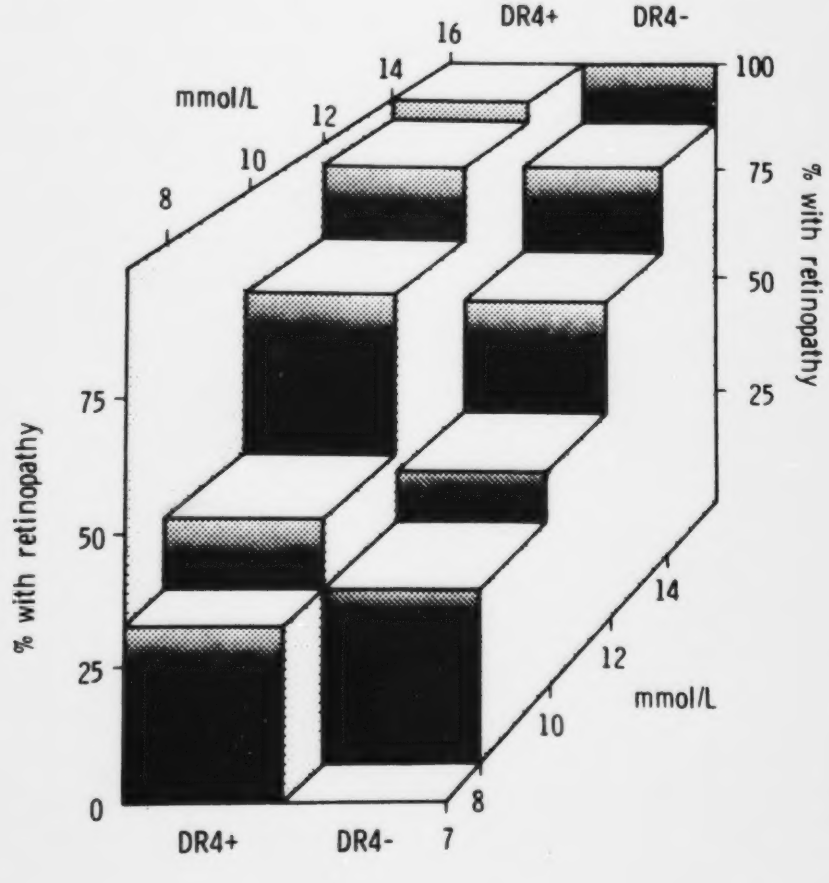


Figure 2. Patients with and without HLA-DR4 have been divided into five groups by mean blood glucose (8.0, 8.0-9.9 10.0-11.9, 12.0-13.9 and 14.0 mmol/L). Within each group the proportion of patients with background of proliferative retinopathy is shown as a percentage (12).

III) consisted of 33 patients with chronic renal failure of diverse etiology other than diabetes. Their ages ranged from 5 to 63 years. Renal sections from patients with diabetes were easily distinguished from those of the other patients and normals by the intense linear staining of extracellular membranes. The most specific reaction was the presence of IgG and albumin lining the tubular basement membrane. Note in Figure 3 the relative specificity of the immunofluorescence in the renal sections from patients with diabetes. Save for some minimal staining of the glomerular basement membrane from the normal kidneys there is practically no overlap among these three groups.

In experimental diabetes in rats, there are exciting data with regard to the role of hyperglycemia and diabetes. First of all similar changes with respect to the immunofluorescent staining for rat IgG and complement C_3 occur after 4-6 months of hyperglycemia. If kidneys from diabetic rats are transplanted into normal rats, the characteristic immunofluorescent lesion disappears in 2 months, (Figure 4) and if kidneys from nondiabetic rats are transplanted into diabetic rats the lesion appears after 2 months (Figure 5).

Finally, if diabetic rats are made normoglycemic by islet cell transplantation, there is regression of the immunofluorescent changes (Figure 6) as well as a reduction in the glomerular volume (Figure 7) as well as a reduction in the percentage of the mesangial volume occupied by the matrix component. (Figure 8)

Figure 3

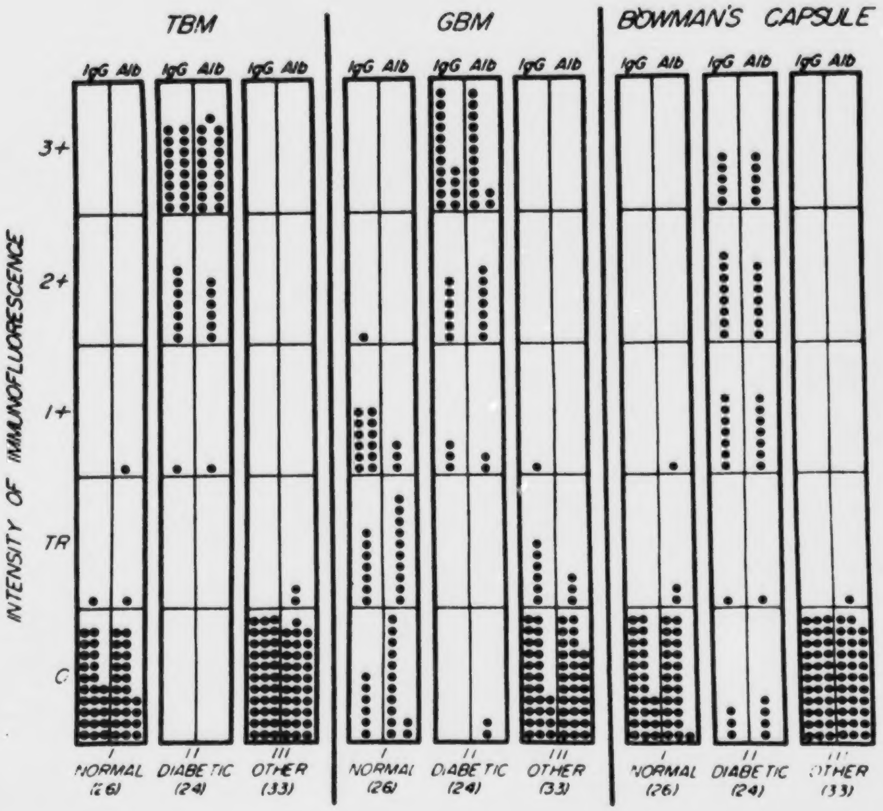


Figure 3. Immunofluorescence for IgG and albumin in tubular basement membranes (TBM), glomerular basement membranes (GBM) and Bowman's capsule in kidneys from normal subjects, and patients with chronic renal failure due to diabetic nephropathy and other renal diseases (39).

Figure 4

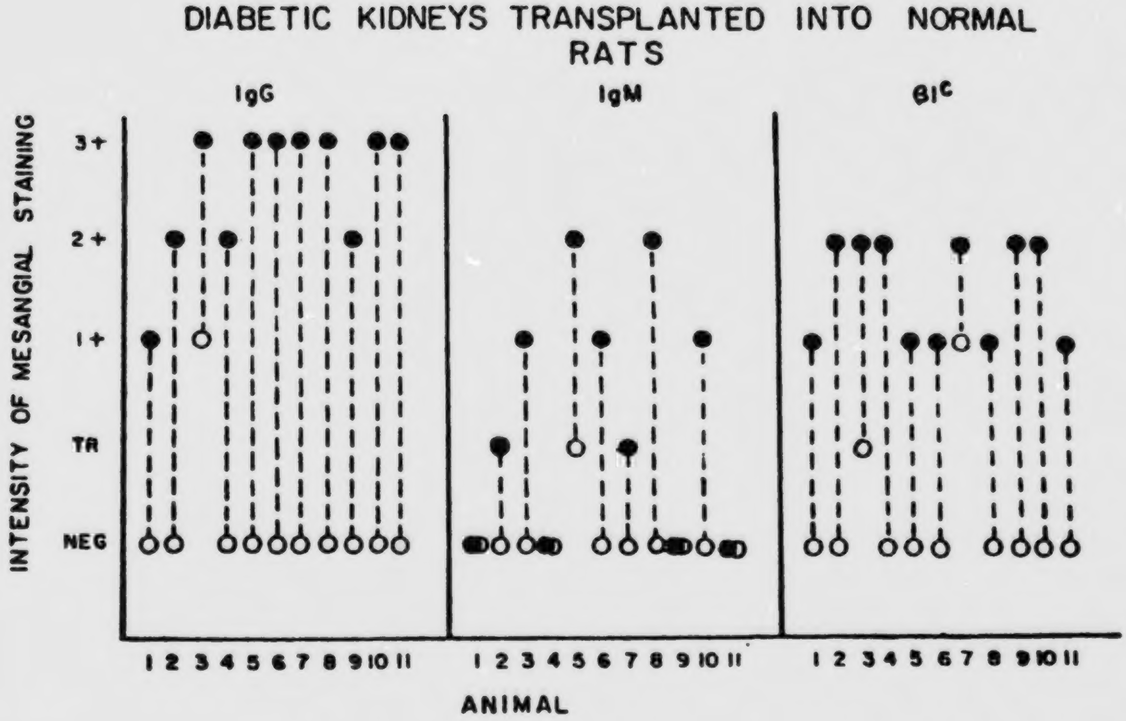


Figure 4. Results of immunofluorescent microscopy studies of kidneys transplanted from diabetic rats into normal recipients; biopsies before transplantation, (closed circle), biopsies 2 months after transplantation, (open circle). (30)

Figure 5

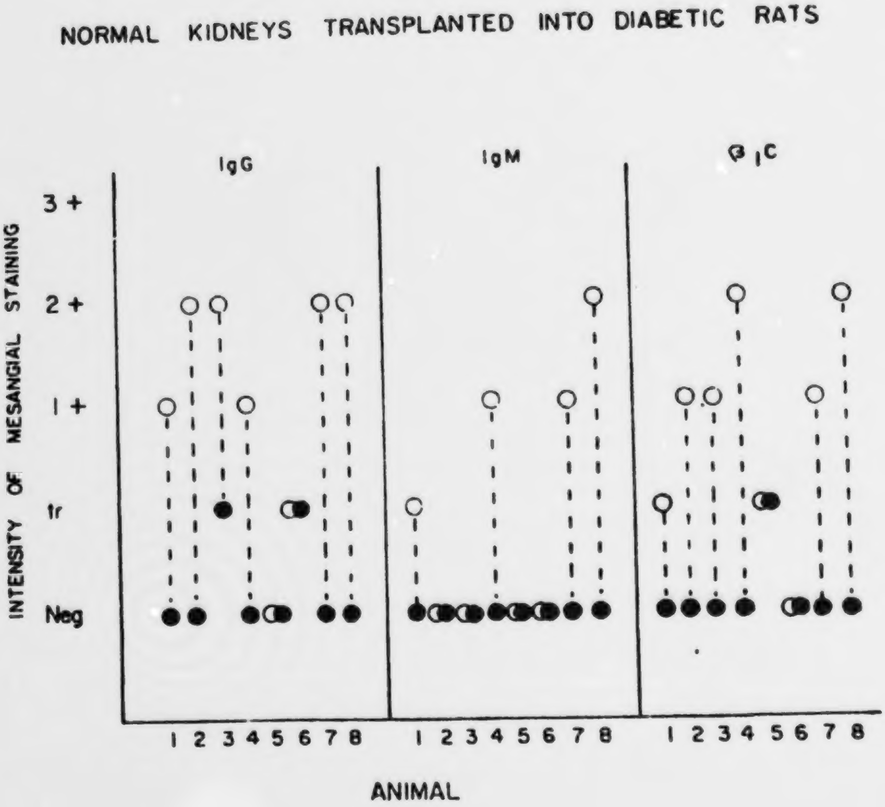


Figure 5. Results of immunofluorescent microscopy studies of kidneys transplanted from non-diabetic rats into diabetic recipients; biopsies before transplantation (closed circle), biopsies 2 months after transplantation (open circle).

Figure 6

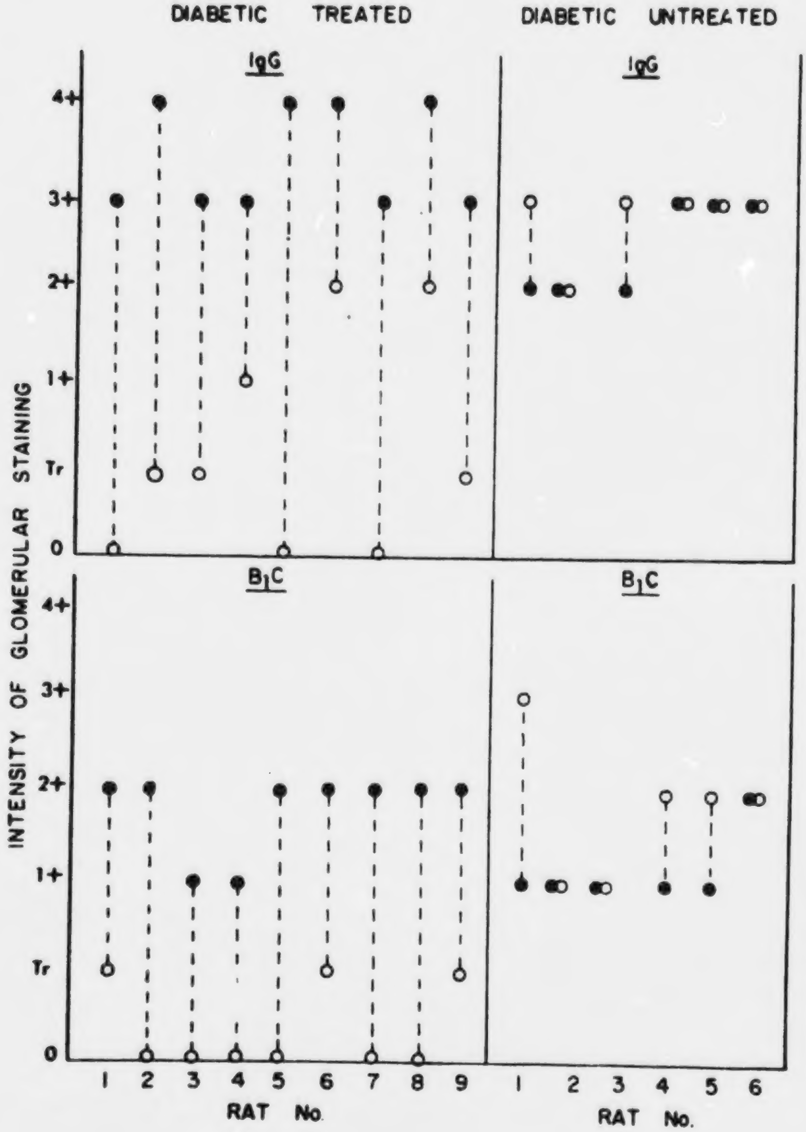


Figure 6. Results of immunofluorescent microscopy studies with staining for rat IgG and B_1C; biopsies before transplantation; (closed circle), biopsies 3 months after transplantation, (open circle) (33).

Figure 7

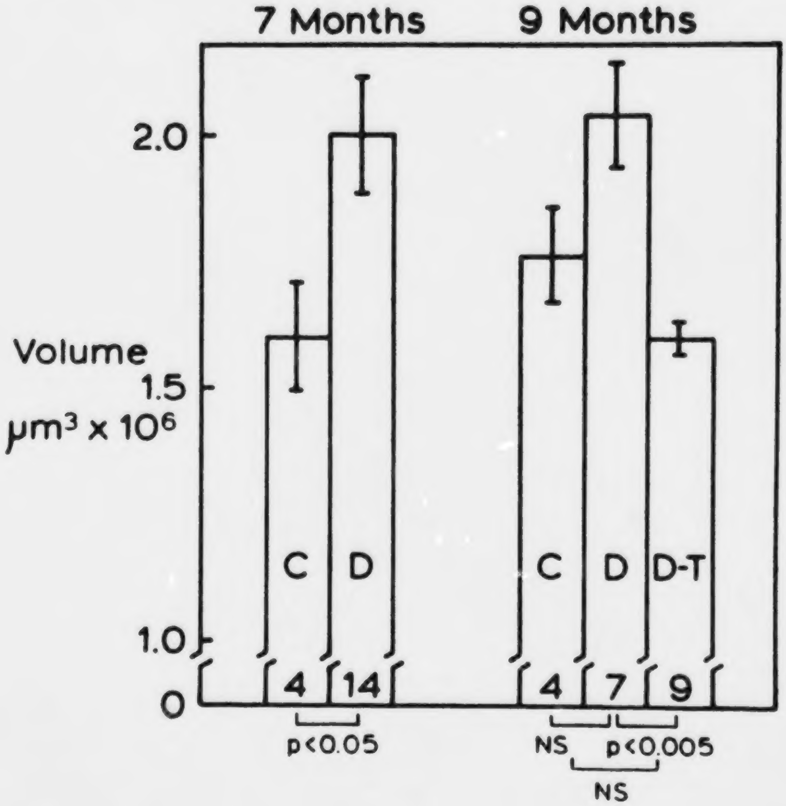


Figure 7. Glomerular volumes at the time of, and 2 months after, islet transplantation (intraportal distribution of neonatal pancreatic tissue after 7 months of diabetes C-control, D-diabetic, D-T-diabetic transplantated.

Figure 8

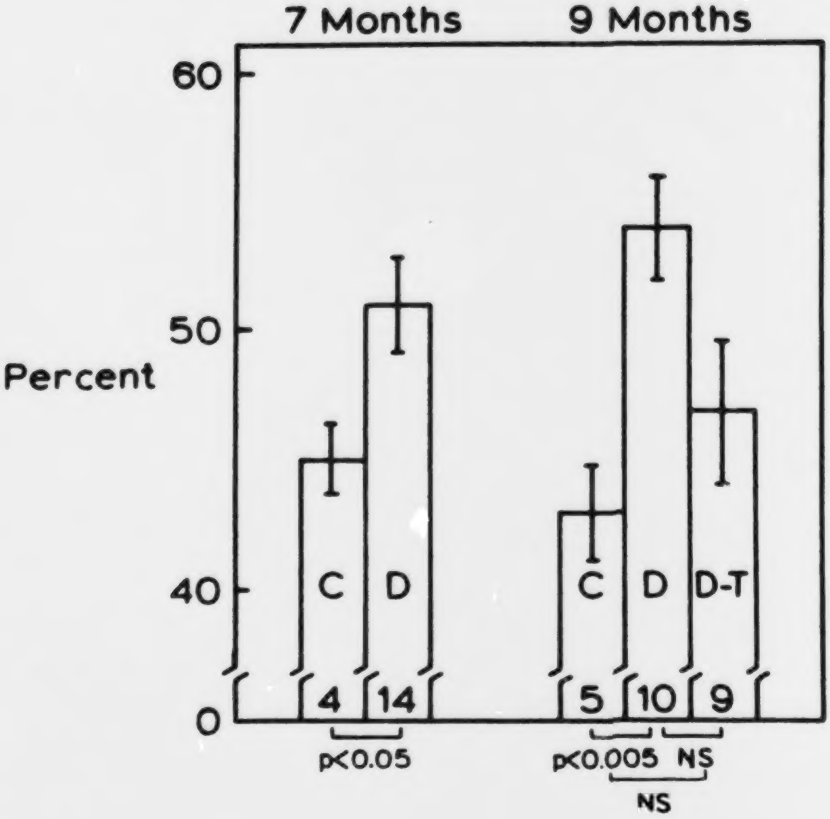


Figure 8. The percentage of the total mesangial volume occupied by the matrix component at the time of and at 2 months after islet transplants (63).

In human beings, experiments of a similar nature have given results very similar to those obtained in the experimental diabetes of animals. Mauer et al, examined kidney tissue obtained from 12 diabetic and 17 non-diabetic patients from 2 to 12 years after renal transplantation. The frequency and intensity of IgG and albumin staining of the tubular and glomerular basement membrane and Bowman's capsule was significantly greater in the diabetic than in the non-diabetic patients. Except for some staining of the glomerular basement membranes in the non-diabetic kidneys, there was practically no overlap between the two groups (Figure 9).

Although 9 of the 12 diabetic patients received their kidney from a living related donor, no immunofluorescence was observed in 7 kidneys studied at the time of their transplantation into diabetic recipients.

This same group studied renal-transplant tissue from 12 diabetic and 28 non-diabetic patients who had a renal graft for at least 2 years. Ten of the 12 kidneys studied from diabetic patients showed arteriolar hyalinosis and in 6 of the 10, the hyaline change involved both the afferent and efferent limb of the glomerular arterioles. One diabetic patient developed typical nodular glomerulosclerosis 35 months after transplantation. Three of the 28 kidneys studied from the non-diabetic transplant recipients had hyaline vascular changes. These occurred only in rare vessels and did not appear until five years post transplantation and never involved both afferent and efferent arterioles. None of the blood vessel changes were present in the kidneys transplanted into the diabetic recipients at the time of transplantation although 10 of the 12 received living related donor grafts.

Figure 9

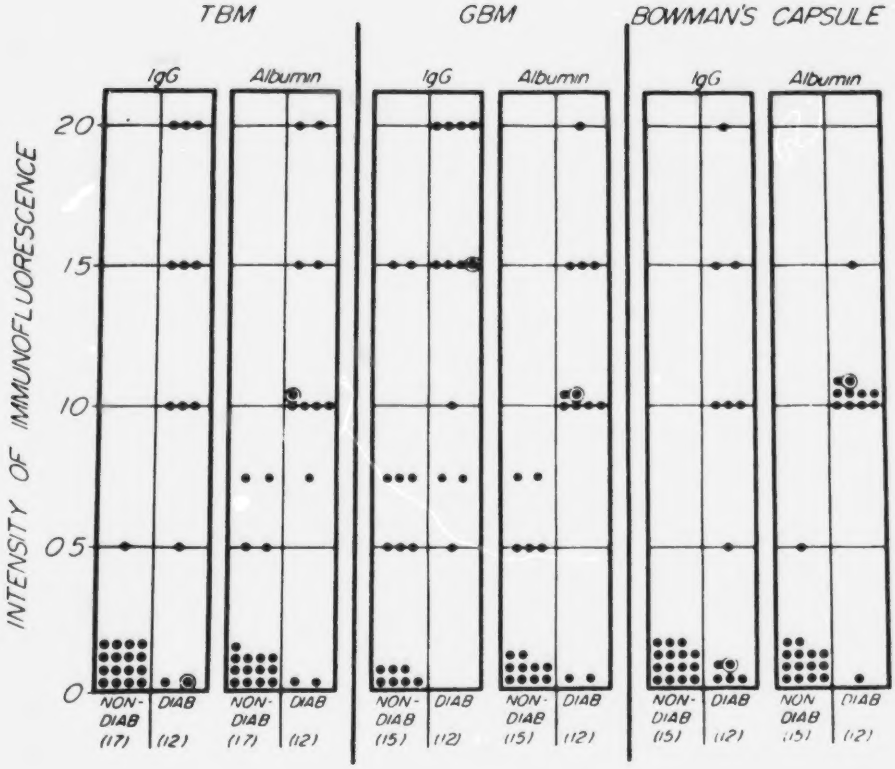


Figure 9. Immunofluorescense for IgG and albumin in tubular basement membrane (IBM), glomerular basement membranes (GBM) and Bowman's capsule of kidneys transplanted into diabetic and non-diabetic patients (37).

Table 5
Incidence Of Lesions Of Arteriolar Hyaline (38)

Group	**Patients With Hyaline Deposits**	
	2-10 Yr After Transplantation	**2-5 Yr After Transplantation**
Diabetic	10 of 12	10 of 12
Nondiabetic	3 of 28	0 of 23
P value*	0.001	0.0005

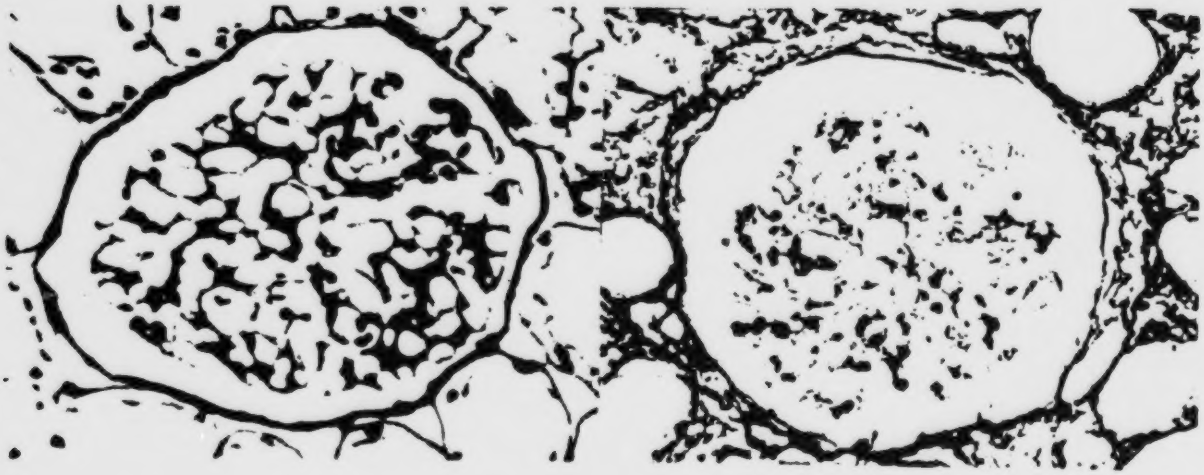
*By chi-square test

There is another interesting human counterpart to some of the studies described above in animals. Kidneys from a 37 year old man with a 17 year history of insulin dependent diabetes were offered for transplantation following his becoming comatose and brain dead. His urine was positive for both glucose and protein. All other laboratory tests were unremarkable. At donor nephrectomy both kidneys were grossly normal. After some difficulty placing the organs, they were finally accepted by a transplant center in Kuwait. Both kidneys were successfully transplanted into two male recipients whose chronic renal failure was due to polycystic kidney disease. After transplantation both kidneys functioned well with standard immunosuppression. At the time of transplantation both kidneys showed features of established glomerulosclerosis and an increase in the mesangial matrix and a thickening of the glomerular capillary basement membranes. Renal biopsy specimens taken 7 months after transplantation showed complete resolution of the light microscopic abnormalities (Figure 10) and both patients had no proteinuria after an additional 7 months of follow-up.

CLINICAL TRIALS

If the metabolic abnormalities of diabetes are in some way responsible in a cause and effect way for the development of microangiopathy then it should be possible to demonstrate that correction of these metabolic abnormalities prevents and/or delays the development of these vascular complications. What follows is a description of clinical trials, whose data bear upon these issues. The first two of these studies are retrospective and thus suffer from all the problems associated with retrospective analysis. Also, there is the problem of the appropriate assessment of overall diabetes control. Most often no objective data are available to judge diabetes control.

Figure 10



BEFORE TRANSPLANTATION AFTER TRANSPLANTATION

Figure 10. Biopsy specimen seven months after transplantation showing (left) widely open glomerular capillaries with almost normal basement membrane and mesangium (PASx400) and (right) almost normal glomerular architecture (methenamine silverx400) (1).

The Malmo Study

Johnsson reviewed all diabetic patients in Malmo, Sweden, whose diabetes was diagnosed between 1922 and 1945 and who were less than 40 years of age at the onset of their disease (20). They were divided into two groups. Series I consisted of 56 patients diagnosed from 1933 to 1935. All these patients were initially treated with strict diet control and multiple daily injections of insulin in an attempt to keep the urine free of glucose. Series II consistedof 104 patients whose disease was diagnosed from 1935 to 1945. These patients were treated with long acting insulin and a much less regimented diet. The patients in Series II had a much higher incidence of vascular complications than did those of Series I.

Table 6 shows that whereas the mean duration of the diabetes for those patients in Series I was 10 years longer than Series II only 32% had nephropathy as compared with 56% in Series II.

Table 6
Incidence Of Nephropathy - Malmo Study (20)

	Series I	Series II
Number of patients	56	104
Duration of diabetes	24.5 years	15.9 years
Patients with Nephropathy	18 (32%)	56 (54%)

The difference is even more striking when one looks at the incidence of nephropathy in patients who have had this disease for more than 15 years (Table 7).

Table 7
Incidence Of Nephropathy In Malmo Study
After 15 Years Of Duration Of Diabetes (20)

	Series I	Series II
Number of patients	56	57
Patients with Nephropathy	5 (9%)	35 (61%)

Only 9% of patients in Series I had nephropathy as compared to 61% of Series II. Similar striking differences were seen between the groups when the incidence of retinopathy was compared. Hypoglycemia was far more common in Series I patients, reflecting attempts to achieve normoglycemia and the use of multiple daily insulin injections.

The Belgian Study (50)

This is perhaps the largest study of its kind. Dr. Pirart has followed 4,398 patients with diabetes from 1947, of which 2,795 patients were followed since the initial diagnosis of their diabetes. Despite the obvious limitation of this study, that of the inability to accurately assess long term diabetes control, Dr. Pirart's data suggest a strong relationship between the level of diabetic control and the development of diabetic complications. Figure 11 demonstrates the prevalence of retinopathy as related to the level of diabetic control over the years of follow-up. It is clear, the higher the level of blood glucose the greater the prevalence of diabetic retinopathy. Of note however, is the the fact almost 30% of Dr. Pirart's patients, despite many years of poor diabetes control, had essentially no diabetic retinopathy.

The Job Study (19)

The study by Job et al, as outlined in Table 8 was designed in a prospective fashion. Diabetic patients were randomly assigned to either a single insulin injection group or a multiple (three times daily) insulin injection group. Both groups were followed for a mean duration of three years. The progression of retinopathy was evaluated by fluorescien angiography and funduscopic examination. They reported a significantly greater increase in the number of microaneurysms in the single injection group as compared to the multiple injection group. Unfortunately, this study suffers from an important defect which makes the result difficult to evaluate. Of those 21 patients whose data were analyzed from the single injection group, only 16 received one daily insulin injection for the entire period of study; the other 5 were changed either to 2 or 3 injections per day after the study began. In the multiple injection group only 5 of the 21 patients analyzed had 3 insulin injections daily for the entire period of the study. The others either initially accepted only 2 injections (4 patients) or some only 1 (4 patients). Nine of the 13 who originally accepted 3 injections daily were reduced to 2 injections after 1 year. The small number of patients initially studied coupled with the many crossovers in the protocol probably make this study invalid.

Figure 11

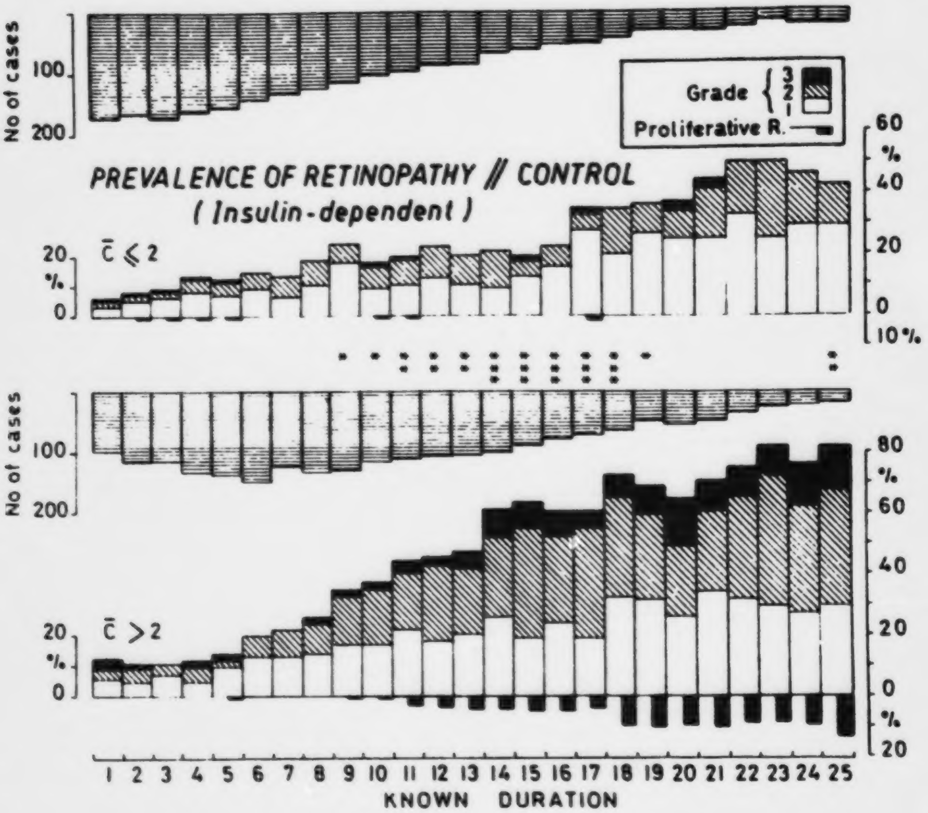


Figure 11. Ascending curves for different grades of retinopathy as a function of duration in severe diabetes with good (top) or with poor cumulative glycemia control (bottom) (50).

Table 8
Comparison Of The Increase In The Number Of Microaneurysms Between The Two Groups (Means ± S.E.M.)

		Single Injection Group	Multiple Injection Group	P. Values
Number of Microaneurysms	-At Baseline	12.7 ± 3.5	9.0 ± 3.3	N.S.
	-At The Last Examination	33.0 ± 7.9	15.2 ± 3.3	0.05
	-Difference	20.3 ± 4.9	6.2 ± 2.5	0.02
Mean Yearly Increase in the Number of Microaneurysms		7.2 ± 1.9	1.8 ± 0.7	0.01 0.02*
Mean Yearly Increase in the Square Root of the Number of Microaneurysms		0.85 ± 0.16	0.24 ± 0.13	0.01

*Nonparametric test. As the variances of the mean yearly increase in the number of microaneurysms differed between the two groups, they were also compared by a nonparametric test (Mann and Whitney) and the square-root transformation, which equalized the variances (19).

Controlled Prospective Trials

As alluded to earlier, the past several years have brought great advances in the treatment of insulin dependent diabetes mellitus. Included in these advances are the use of innovative treatment strategies such as multiple insulin dosage programs, portable insulin infusion devices, and the increased use of the self monitoring of blood glucose. As a result of these advances it has been possible to design appropriate prospective studies to evaluate more fully in human beings the relationship between diabetic control and complications. The following are the results of some of these studies.

The Steno Study (28)

In this study 30 insulin dependent diabetic patients with background retinopathy were given random assignment of either conventional treatment (UCT) (2 daily injections of insulin) or treatment with conventional subcutaneous insulin infusion (CSII) and followed prospectively for more than 2 years. Retinal examinations were done at 6 month intervals. Mean blood glucose levels and stable hemoglobin Al_c values were significantly lower in the CSII treatment group than the UCT treatment group. Retinal morphology deteriorated during the first year in both groups but there were no significant differences between the two. However, the frequency of deterioration was highest in the CSII group, especially among the patients with the best glycemic control. Retinal function (oscillatory potential, macular recovery time, and posterior vitreous fluorophotometry) improved significantly with CSII treatment and deteriorated significantly with conventional treatment. Changes in retinal function were most pronounced in patients with the best and the poorest diabetic control. Table 9 shows the results of steno fundus photographs revealing that despite the apparent, although not statistically significant, deterioration of retinopathy after the first year of the study, there appears to have been a levelling off after 2 years of follow-up. There are now several studies reported that have shown a tendency toward an acceleration of diabetic retinopathy in patients treated intensively. The mechanism by which this hopefully reversible deterioration occurs is unknown.

Table 9
Steno Study
Fundus Photographs (28)

	1 Year		**2 Years**	
	CT	**CSII**	**CT**	**CSII**
Improved	3	3	2	7
No Change	7	2	2	2
Worse	5	10	10	6

In this same study, the effect of diabetic control on glomerular filtration rate and urinary albumin excretion rate was also evaluated. They showed that glomerular filtration rate can be reduced and frequently normalized with prolonged metabolic control, but this does not occur in patients on conventional treatment whose diabetes control is stable though unimproved. There were no effects on urinary albumin excretion with either treatment (Table 10).

Figure 12

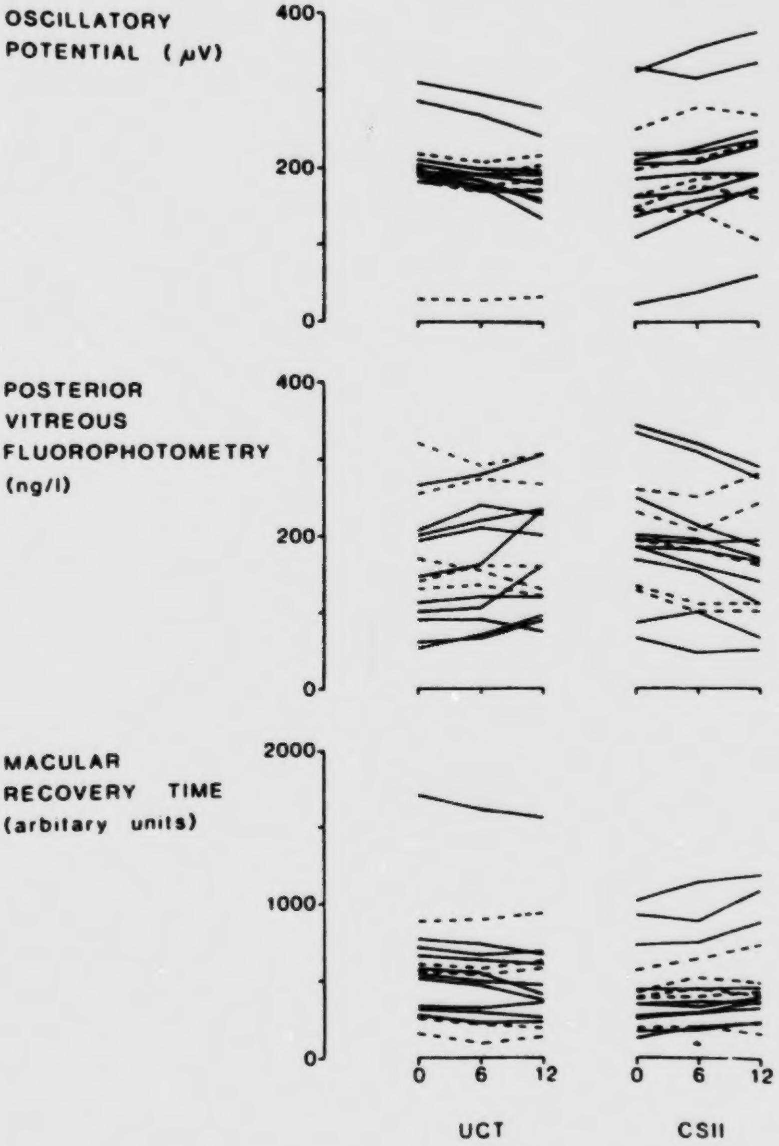


Figure 12. Oscillatory potential posterior vitreous fluorophotometry, and macular recovery time for UCT and CSII patients. In the UCT panel solid lines indicate the ten poorest regulated patients and in the CSII panel solid lines indicate the best regulated patients. In both panels broken lines represent intermediately regulated patients. Each line represents the measurement for one patient at 0, 6, and 12 months. Shaded area indicates normal range (mean ±2SD) (28).

Table 10
Steno Study (28)
Renal Function Studies

	Glomerular Filtration Rate (ml/min x 1.73m^2)			Urinary Albumin Excretion Rate micro-g/min		
	0	1 Year	2 Years	0	1 Year	2 Years
CSII	131 ± 5**	117 ± 5	111 ± 4*	36 ± 9	43 ± 14	79 ± 43
CT	114 ± 4	112 ± 4	112 ± 5	62 ± 18	195 ± 8	267 ± 98*

* = p 0.05.2 years vs baseline
** = p 0.05 CSII vs CT

There are several other studies that report similar results, i.e., little or no improvement in renal function despite several years of improved diabetes control. It appears that once significant diabetic renal disease develops improved diabetic control does not cause reversal or even a slowing of the rate of progression. It is of importance to mention here that aggressive management of patient's hypertension has been shown to be beneficial in terms of slowing the progression of diabetic renal disease.

The British Study (18)

In this study conducted at diabetic clinics at Oxford and Aylesbury, 174 insulin-dependent diabetic patients with background retinopathy were randomized to continue with usual diabetic care (Group U) or to a more intensive program (Group A) using Ultralente insulin as basal cover and soluble insulin before meals. In addition, Group A attended the clinic more frequently, received closer dietary supervision, and were taught self blood glucose monitoring. Group A had a significantly lower mean glycosylated hemoglobin level during the study, although the mean levels also fell in Group U towards the end of year 2. (Figure 13). Renal and sensory nerve functions were significantly better preserved in Group A than in Group U (Figure 14). The rate of progression of retinopathy was similar in both groups. It was concluded that a modest improvement in diabetic control obtainable in most clinics is associated with a reduction in the progression of diabetic tissue damage.

Figure 13

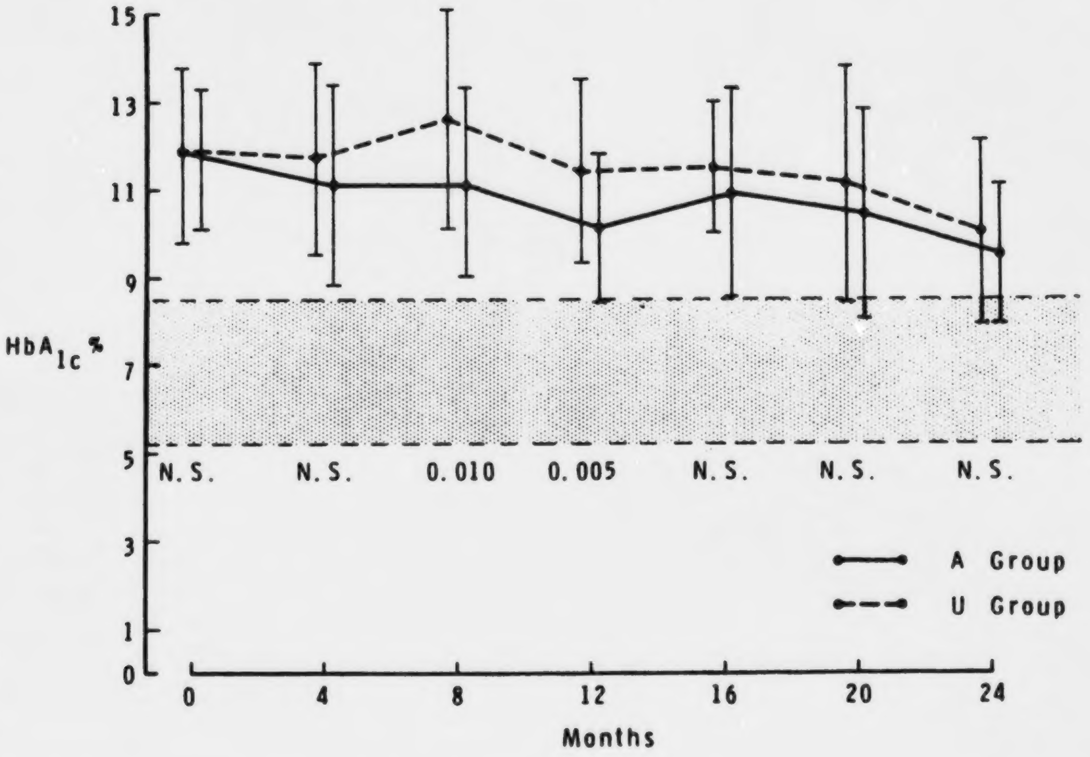


Figure 13. Mean HbA$_{1c}$ levels (± SD) in each group. Shaded area = normal range. NS - not significant (18).

Figure 14

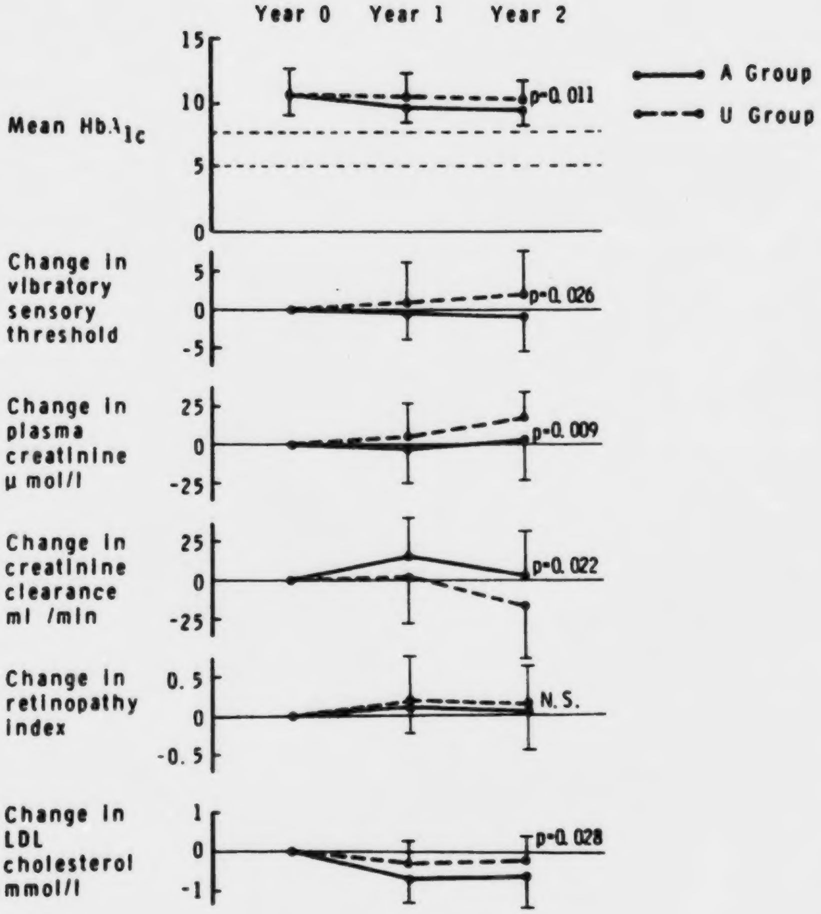


Figure 14. Changes from entry (year 0) to year 1 and to year 2. With the exception of HbA_{1c} for which values are given at entry and the mean of all values (excluding entry) over year 1 and over 2 years (18).

The New Haven Study (51)

In this study 30 eyes of 15 type 1 diabetic patients were evaluated prospectively before and after 11-23 months (mean 18.1 months) of pump treatment. In each patient plasma glucose and total glycosylated hemoglobin levels fell to normal or near normal levels. The 10 eyes without diabetic retinopathy at entry remained without. Four of 20 eyes with diabetic retinopathy at entry advanced by modified Early Treatment Diabetic Reinopathy Study (ETDRS) classification, including one eye that progressed from background to proliferative diabetic retinopathy. No eyes with diabetic retinopathy improved their modified ETDRS classification. One eye progressed to blindness; no other eye lost vision. Six eyes had laser treatment prior to insulin pump treatment; four of these and two more required laser treatment during pump treatment. Two eyes had vitreous hemorrhages prior to pump treatment; one of these and four others hemorrhaged during pump treatment. No eyes with diabetic retinopathy showed regression of microvascular changes (Table 11). The data suggested to the authors that prolonged restoration of near normal glucose metabolism with the insulin pump does not reverse established diabetic retinopathy (Figure 15)

Table 11
Summary Diabetic Retinopathy Classification (51)
(30 Eyes Of 15 Patients)

	Entry	**Current**
Number of diabetic retinopathy	10	10
Background retinopathy	9	8
Proliferative retinopathy	11	12
Total Eyes	30	30

Figure 15

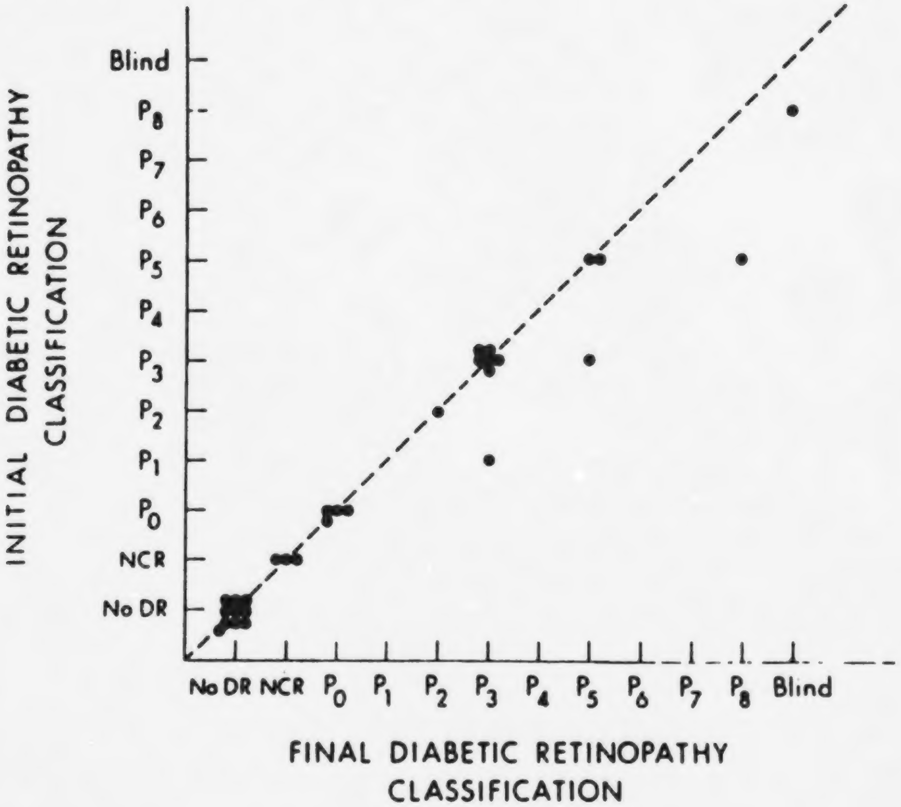


Figure 15. A scatter diagram plotting the initial modified ETDRS classification of each eye on the ordinate with the final modified ETDRS classification on the abscissa. Dots falling on the 45° line represent no change; those below the line represent a progression of retinopathy (51).

The Kroc Study (26)

This is a prospective multicenter trial whose data have been recently reported. In this study patients with nonproliferative diabetic retinopathy and absent C-peptide were randomly assigned to pump (n=35) or conventional therapy (n=35). Subsequently, glycemic control and retinopathy (fundus photography and fluoroscein angiography) were periodically assessed over 8 months. At the start of the study, age duration of diabetes, insulin dose, glycemic control, and the degree of retinopathy were similar in the 2 groups. After randomization, mean blood glucose (175 ± 9 mg/dl) and glycosylated hemoglobin levels (10.0 ± 0.3%) remained elevated in the conventional treatment group, but fell to near normal values (117 ± 6 mg/dl, 8.1 ± 0.3% respectively) during the entire period of pump treatment (p 0.001 vs. conventional treatment group) (Figure 16).

The frequency of biochemical hypoglycemia was similar in both studies, but ketoacidosis occurred only with pump therapy. The level of retinopathy assessed from photographs progressed in both groups. Continuous subcutaneous insulin infusion was associated with slightly more deterioration in diabetic retinopathy as compared to the conventionally treated group, mainly because of the appearance of soft exudates and intraretinal microvascular abnormalities (Figure 17). In contrast, elevated albumin excretion rates fell during continuous insulin infusion but not conventional treatment (Figure 18). The conclusion from this study is that a nearly normal blood glucose level for 8 months does not retard progression of, and in fact may initially worsen, established retinopathy. They suggested the need for longer trials, particularly directed toward primary prevention.

Figure 16

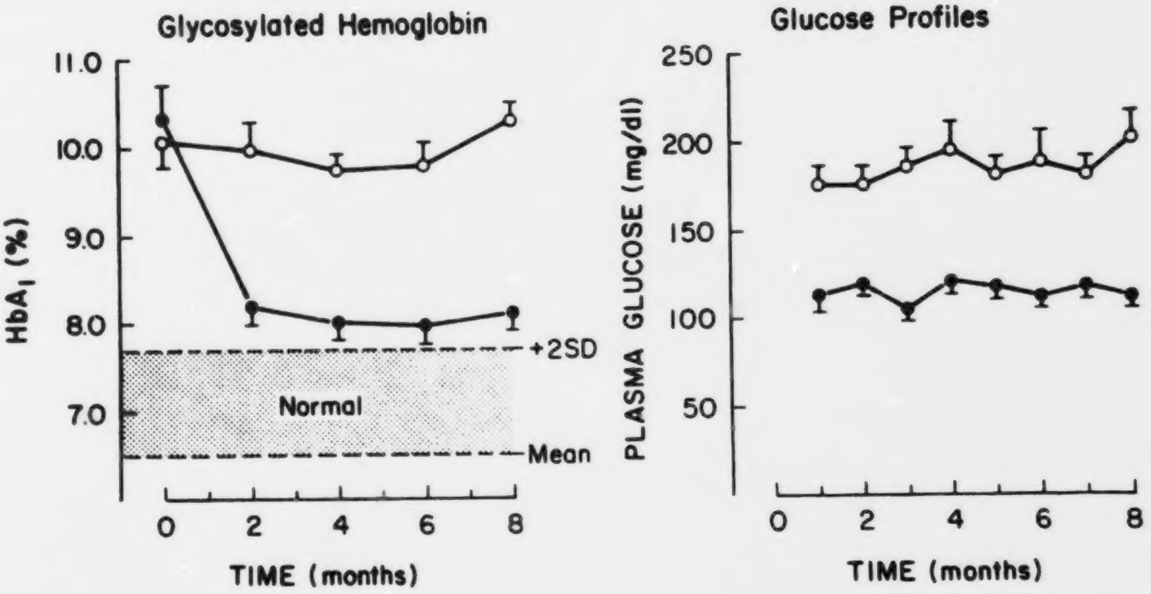


Figure 16. Home assessments of glycemic control in patients randomly assigned to continuous subcutaneous insulin infusion (closed circle) or unchanged conventional injection treatment (open circle) (26).

Figure 17

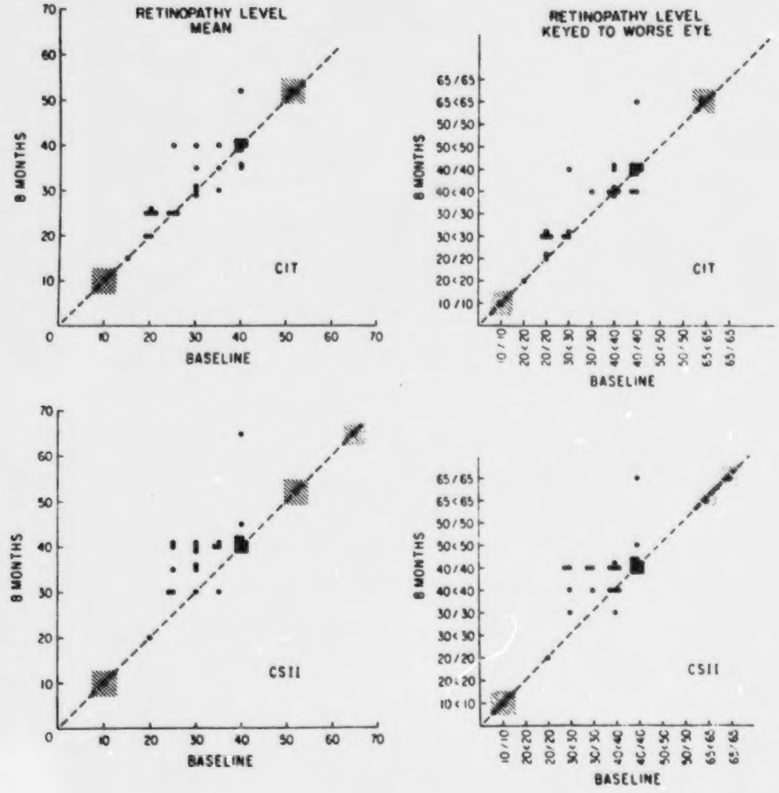


Figure 17. Retinopathy levels at baseline and at 8 months in individual patients assigned to CSII or CT (26).

Figure 18

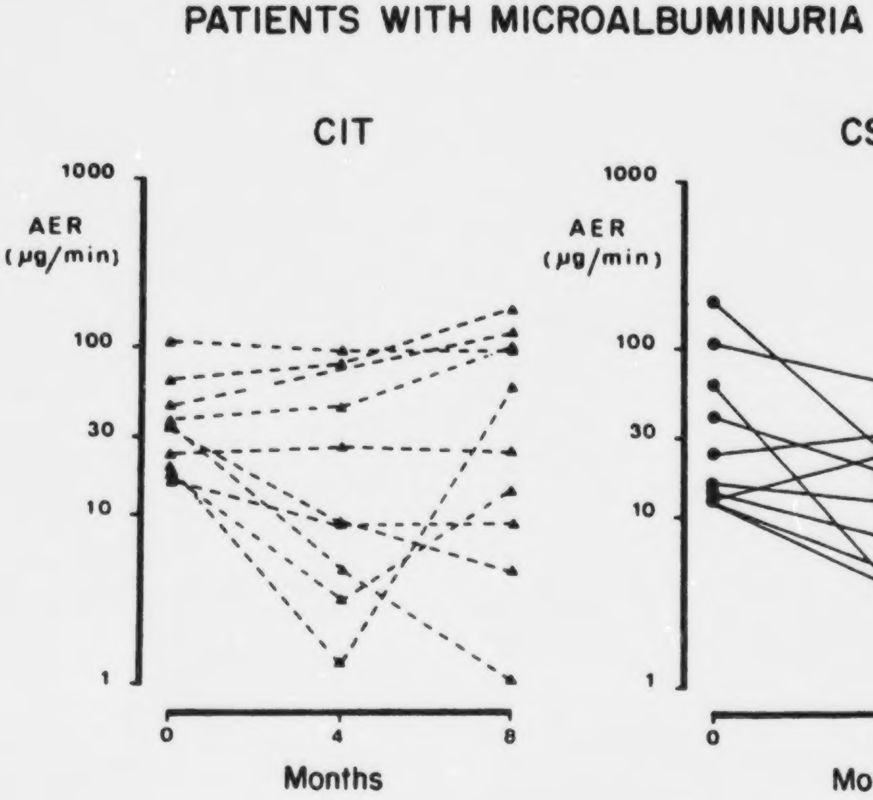


Figure 18. Changes in albumin-excretion rate in the 10 patients in each treatment group with supranormal baseline values (exceeding 12 micrograms per minute) (26).

The Dallas Study (56)

Over the past several years Raskin and his co-workers have been engaged in a prospective non-randomized trial of the effect of an experimental treatment program on diabetic complications in insulin dependent diabetic patients (C-peptide negative). This treatment program includes aggressive dietary instruction, self blood glucose monitoring, and continuous subcutaneous insulin infusion delivered via a portable insulin infusion device. Data from this group of patients have been compared to a similar group of type 1 diabetic patients who preferred to continue with their more conventional diabetes treatment rather than accept entry into the experimental treatment program. Over the years they have shown considerable advantage from the experimental treatment program over conventional treatment with respect to many metabolic parameters such as plasma glucagon profiles, lipid and lipoprotein levels and motor nerve conduction velocities.

They have also measured skeletal muscle capillary basement membrane width in 51 of these patients in whom observations have been made from 1 to 3 years. On these 51 patients, 26 accepted our offer to enter the Experimental Treatment Group and 25 were in the Conventional Treatment Group. Data from diabetic patients were compared with those of a group of non-diabetic subjects, 43 of whom had glycosylated hemoglobin determinations and 21 of whom agreed to undergo a muscle biopsy for measurement of skeletal muscle capillary basement membrane width.

During the 3 years of improved diabetic control reflected by a decrease in glycosylated hemoglobin levels, using an experimental treatment program consisting of rigid dietary control, self blood glucose monitoring and continuous subcutaneous insulin infusion there is a significant reduction in skeletal muscle capillary basement membrane width (Figure 19). This reduction is not evident in the group of diabetic patients treated with a more conventional program who showed a stable, though unimproved, level of diabetic control (Figure 20). If capillaries in skeletal muscle are reflective of those in retinal and/or renal tissue, then meticulous diabetic control for prolonged periods might be beneficial with respect to the microvascular complications of diabetes.

Figure 19

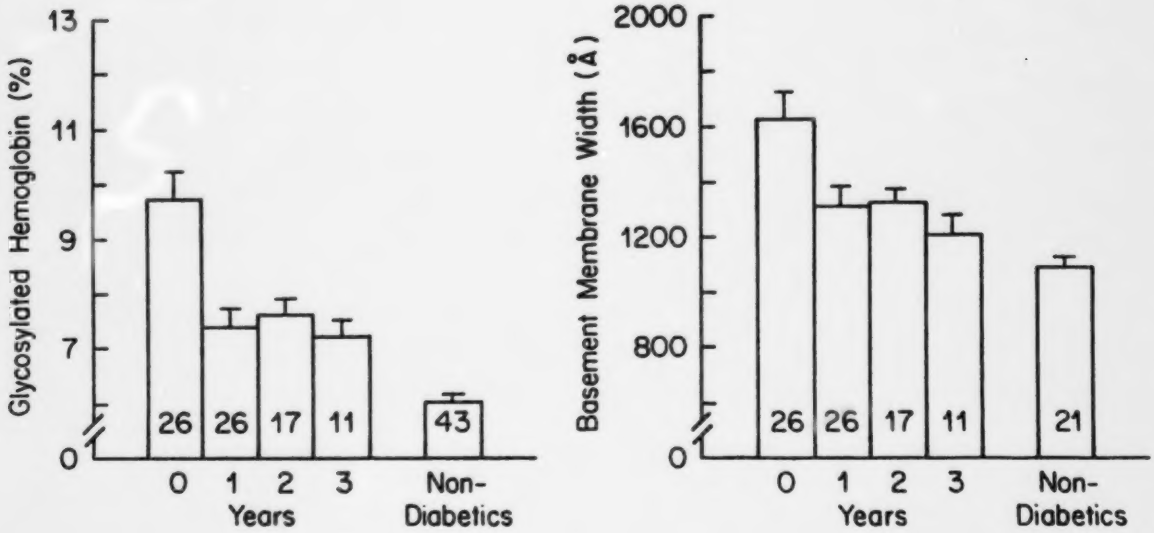


Figure 19. Quadriceps capillary basement membrane width and glycosylated hemoglobin levels in Type I diabetic patients in the Experimental Treatment Group. Values in nondiabetics are included for reference (Raskin et al, 1983) (56)

Figure 20

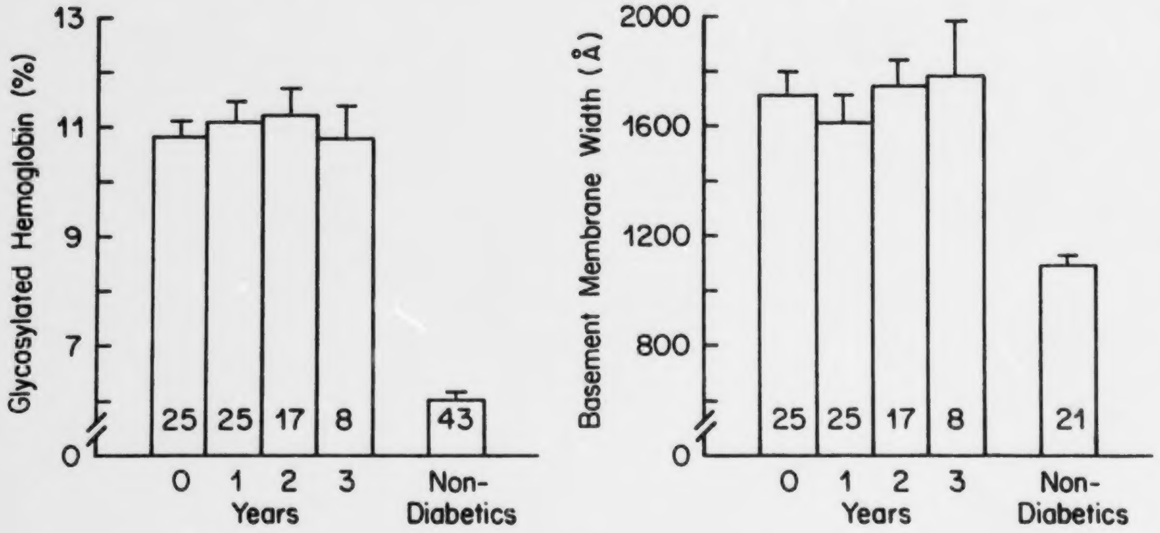


Figure 20. Quadriceps capillary basement membrane width and glycosylated hemoglobin levels in Type I diabetic patients in the Conventional Treatment Group. Values in nondiabetics are included for reference (56).

Figure 21

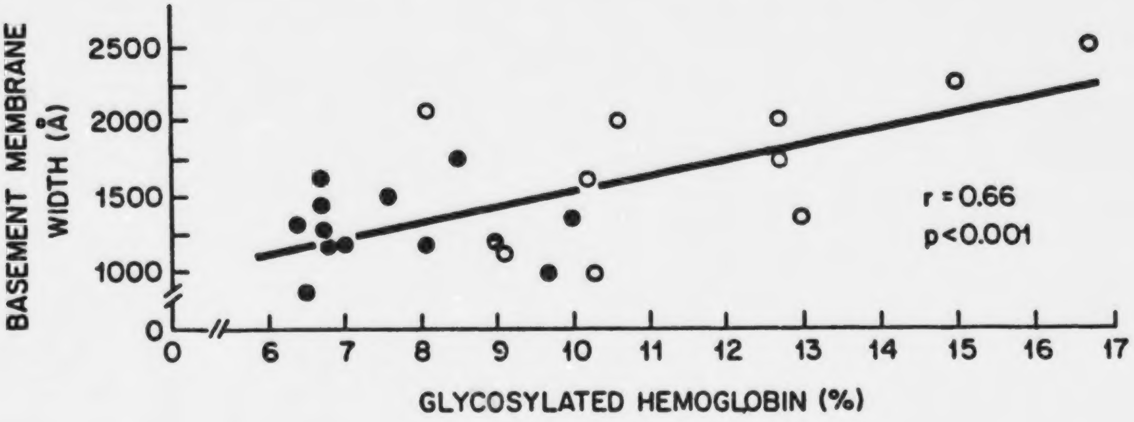


Figure 21. The relationship between capillary basement membrane width and glycosylated hemoglobin values in Type I diabetic patients after 2 years of treatment (56).

The Diabetes Control and Complications Trial (DCCT)

This trial is the largest and most ambitious clinical trial to date. The multi-center study consists of twenty-two clinical groups, nineteen of which are in the United States and two in Canada. They plan to follow two large groups of insulin dependent diabetic patients for as long as 8-10 years. These patients will be assigned to treatment on a random basis. One group will receive the standard conventional form of diabetes treatment, the other an intensive experimental treatment designed to achieve euglycemia. The endpoint will be early diabetic retinopathy. This trial, if it continues as planned, should provide an unequivocal answer to this issue.

Conclusions

What are the overall conclusions to be drawn from the data presented. Which of the two hypotheses of the etiology of the microvascular complications of diabetes was the better supported? Given all the facts, it is difficult to come to a single answer. Alternatively, the small blood vessel complications of diabetes may be related to both genetic and metabolic influences. Figure 22 is an attempt to show the interrelationship between genetic and metabolic factors in the development of diabetic complications.

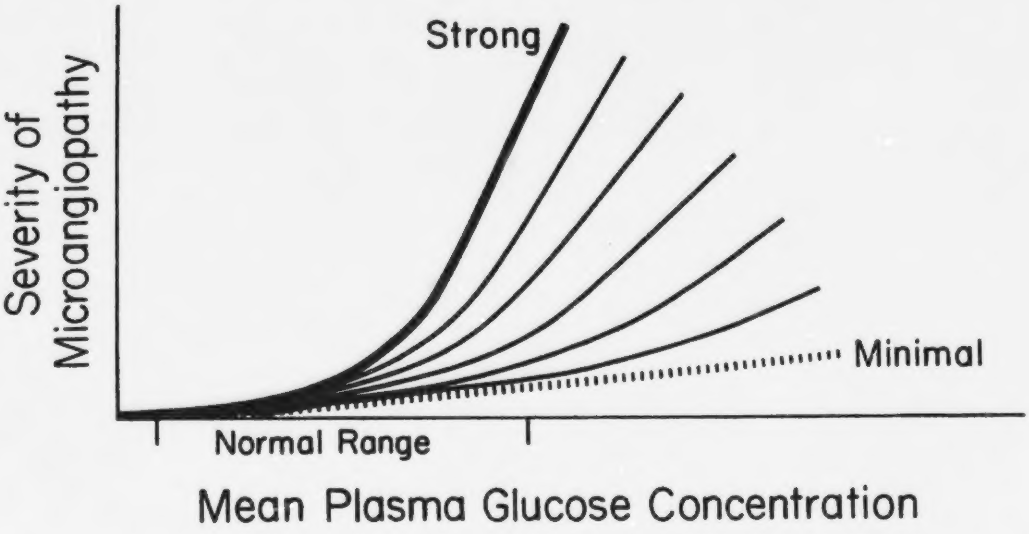
Influence of Genetic Predisposition on the Severity of Diabetic Microangiopathy

In perhaps 20-25% of diabetic patients the genetic predisposition to develop diabetic complications is very low. Thus, no matter how severe the metabolic abnormality, i.e., how much hyperglycemia the patients have over the lifetime of their illness, they rarely develop significant complications. If we could identify this subset of patients at the beginning of their disease our treatment recommendations would be simple. Keep them free of symptoms and avoid both hypoglycemia and severe hyperglycemia and ketoacidosis. These people would not need expensive intensive diabetes management that results in a higher impact on people's lifestyle. In another 5% of patients the genetic predisposition to the development of diabetic complications is so great that even a slight degree of hyperglycemia results in severe microvascular complications. Unfortunately, given our present treatment techniques, we may be unable to normalize completely the blood glucose level sufficiently well enough to help this group of patients. Finally, we have the large bulk of diabetic patients who have varying degrees of the genetic predisposition to develop the microvascular complications. I think that in this group improved diabetic control, that results in a lowering of the overall blood glucose level, might reduce the severity of the microvascular complications.

All of this remains to be proven. Although the data seem to support the suggested synthesis it is not yet a proven fact. In those patients for whom we can do some good by intensive diabetes treatment with resulting long-term near-normal or normal glycemia this should be considered as preventive in nature. It is possible that all we can do is prevent diabetic complications from occurring but that once significant diabetic complications has occured no degree of normoglycemia will cause a reversal.

It must be recognized however, that aggressive diabetes treatment should not be recommended for all patients with insulin dependent diabetes mellitus in the face of not having a definitive answer to this question, since there are in fact several complications to this type of treatment. First of all it is very expensive both to the patient and to the health care systems in general. Finally there is the ever present danger of insulin induced hypoglycemia that can have lethal consequence. Thus, we still must be careful whom we enter into an intensive diabetes treatment program.

Figure 22



INFLUENCE OF GENETIC PREDISPOSITION ON THE SEVERITY OF DIABETIC MICROANGIOPATHY

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DIABETIC RETINOPATHY

Emily Y. Chew, M.D.

Epidemiology of Diabetic Retinopathy

In planning an effective, well-coordinated health-care delivery system, it is important to obtain accurate data concerning the prevalence and severity of diabetic retinopathy, a microvascular complication which can potentially threaten vision. Identifying the patient who may be at risk of developing severe retinopathy is important to ensure optimum ophthalmic care as well as in planning for future studies on the treatment of diabetes and of diabetic retinopathy.

Thus far, a study of the epidemiology of diabetic retinopathy in Canada is not available. However, a population-based study was performed recently in southern Wisconsin in which the prevalence and severity of diabetic retinopathy and the frequency of visual impairment in the total population of diabetics were determined (1,2). The patients were recruited through the physicians who provided primary diabetic care rather than through ophthalmologists, thus decreasing the risk of biasing the selection of patients towards those with ocular symptoms (Figure 1). This diabetic population may be comparable to that found in Canada.

The study also attempted to evaluate the relationships between risk factors, presence and severity of diabetic retinopathy in these patients. In addition to a complete ocular examination with stereo fundus photography, blood pressure measurements, glycosylated hemoglobin, blood glucose and urinalysis were performed. The fundus photographs were graded randomly and independently by several graders using a modified Airlie House classification of diabetic retinopathy (3).

Figure 1

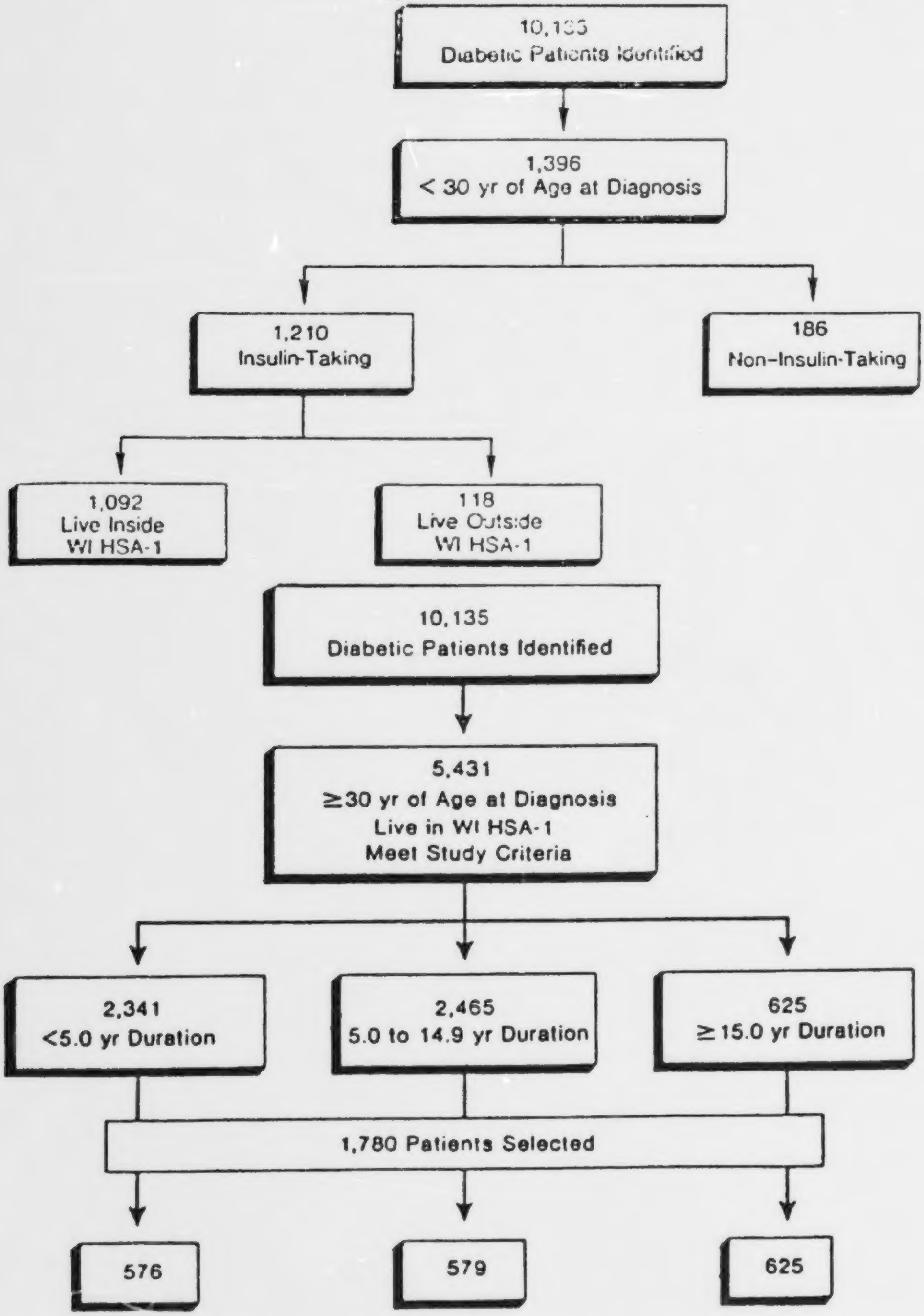

10,135
Diabetic Patients Identified
1,396
< 30 yr of Age at Diagnosis
1,210
Insulin-Taking
186
Non-Insulin-Taking
1,092
Live Inside
WI HSA-1
118
Live Outside
WI HSA-1
10,135
Diabetic Patients Identified
5,431
≥30 yr of Age at Diagnosis
Live in WI HSA-1
Meet Study Criteria
2,341
<5.0 yr Duration
2,465
5.0 to 14.9 yr Duration
625
≥15.0 yr Duration
1,780 Patients Selected
576
579
625

Figure 1. Schematic diagram patient selection for examination phase of study. WI HSA - 1 indicates Wisconsin Health Service Area 1.

The diabetic population was divided into two groups based on the age of onset, whether less than 30 years of age or 30 years of age and older. The results of the study performed in the younger onset group show an increase in frequency of retinopathy with increasing duration of diabetes (Figure 2).

The prevalence rose sharply from 2.2% in those with diabetes of less than 2 years duration to 97.5% in those with diabetes of greater than 15 years duration. The frequency of proliferative diabetic retinopathy increased from 0 in those with diabetes of less than 5 years to about 4% in those with 15 years duration and to 67% in those with 35 years duration (Table 1).

A positive association was found between age and the severity of retinopathy. Retinopathy of moderate severity or worse was present in 10% of the patients age 15-19 years, 41% of the patients aged 20-29 years, 50% of the patients aged 30-44 years and 70% of the patients 45 years or older (Table 2).

In this group of patients with diabetes of more than 10 years duration, the presence of proteinuria and raised diastolic blood pressure was significantly associated (p less than 0.001) with severity of retinopathy. Control of hypertension may be a useful adjunctive therapy in attempting to prevent or reduce severe retinopathy in patients with diabetes of more than 10 years duration.

The group of patients with onset of diabetes at age 30 years or older was the second population evaluated. The ratio of the older onset to the insulin-taking younger onset patients was 5.0. Again the duration of diabetes in these patients was strongly associated with frequency and severity of retinopathy. The overall frequency of retinopathy was 28.8% with proliferative retinopathy occurring in 2% of the patients with diabetes of less than 5 years duration. Thus, the patients with onset at an older age may develop proliferative retinopathy at a much earlier stage of their disease. This may reflect the fact that the time of diagnosis may not coincide with clinical onset.

Table 1
Young-Onset Diabetes
Proliferative Diabetic Retinopathy (1,2)
(PDR)

Duration of Diabetes (yrs)	Prevalence of diabetes
5	0
10	4%
15	25%
35	67%

Table 2
Retinopathy Of Moderate Severity (1,2)

Age of patient (yrs)	Prevalence
15-19	10%
20-29	41%
30-44	58%
45 and over	70%

Figure 2

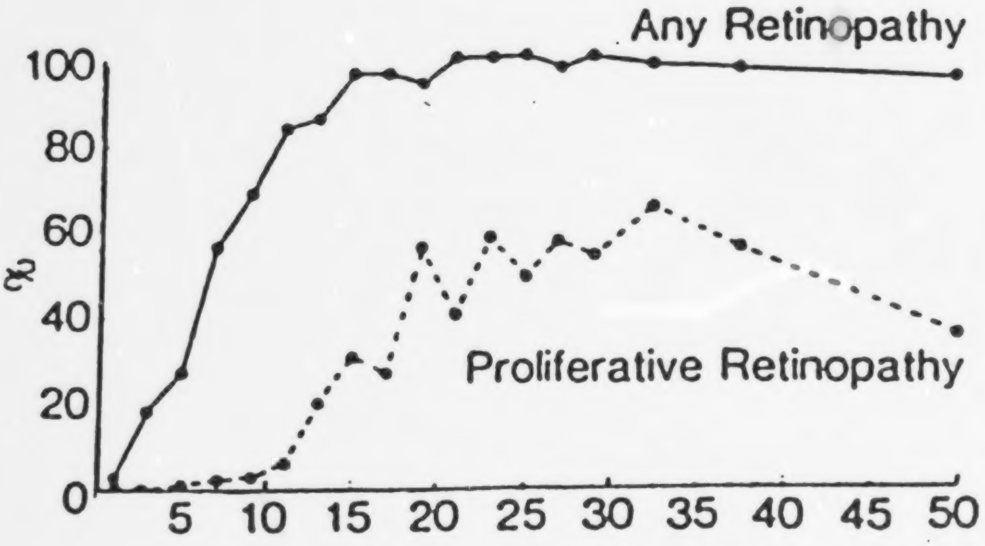


Figure 2. Frequency of retinopathy or proliferative retinopathy by duration of diabetes in years.

In both insulin and non-insulin taking patients, the increased glycosylated hemoglobin was associated with increased risk of retinopathy. This association does not prove the causative effect of good control. Younger onset diabetic patients who received insulin had had diabetes longer, and had poorer control of glucose levels than the non-insulin dependent group. This may reflect the use of insulin as a measure of disease severity rather than insulin being an important factor in the development of retinopathy.

Systolic blood pressure is independently and strongly related to the severity of retinopathy in the older onset group. The presence of proteinuria is also associated with severe retinopathy. Both factors may reflect generalized microvascular disease of diabetes.

The prevalence of macular edema in the population was also provided by this major study (4); 11.1% in the younger onset group and 8.4% in the older onset group. In the younger onset group, macular edema was uncommon in the first 10 years of diabetes, but increased to 32% in patients with 30 or more years of diabetes (Figures 3 and 4).

Visual impairment in diabetes is considered a major cause of blindness in the United States (5). The frequency of visual loss in this study again shows a strong relationship between diabetes, and visual impairment in both the older and younger groups (6). In the younger group, after 30 years of diabetes, 22% of the population had some degree of visual impairment. Legal blindness occurred in 3% of the population of diabetes from 15-19 years. After 30 years duration the prevalence increased to 12%. In the older onset group, legal blindness was found early in the course of diabetes, 0.6% during the first 5 years of the disease while those patients with long-term duration had less legal blindness than those of the younger onset group (Figure 5). In the older onset patients, for eyes with no diabetic retinopathy, 18% of the eyes were visually impaired due to other disease such as cataract and age-related macular degeneration.

Figure 3

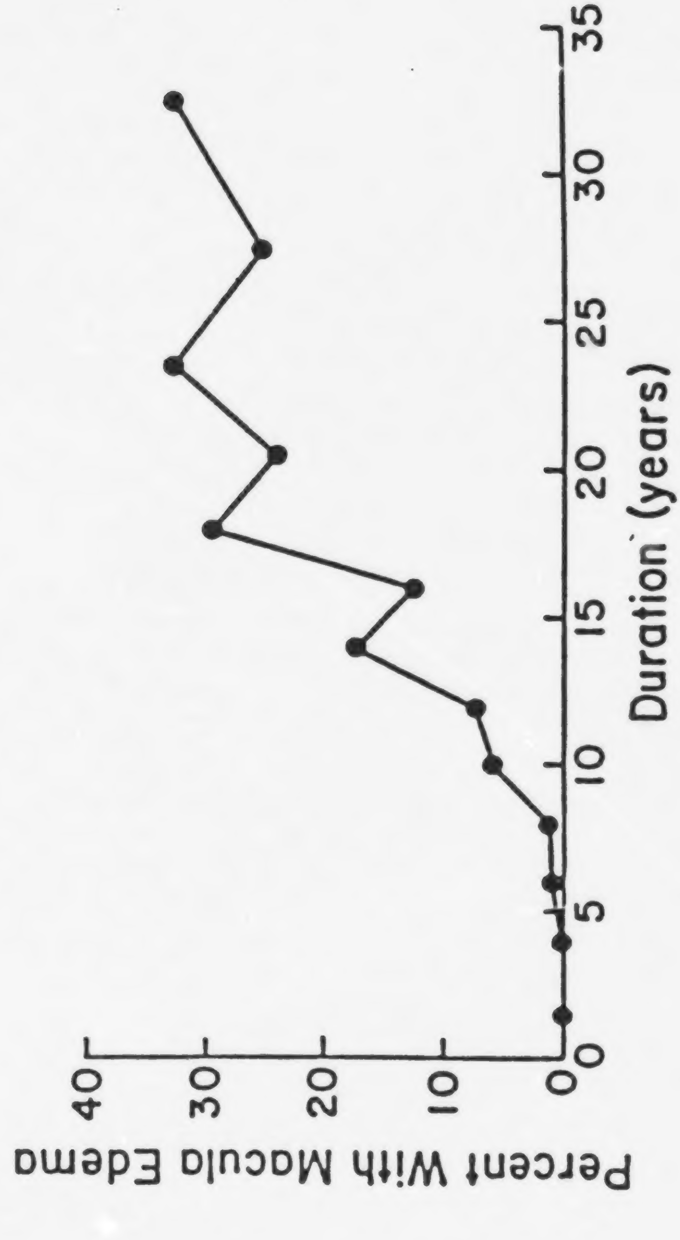


Figure 3. The frequency of macular edema by duration of diabetes in years for insulin-taking younger onset persons.

Figure 4

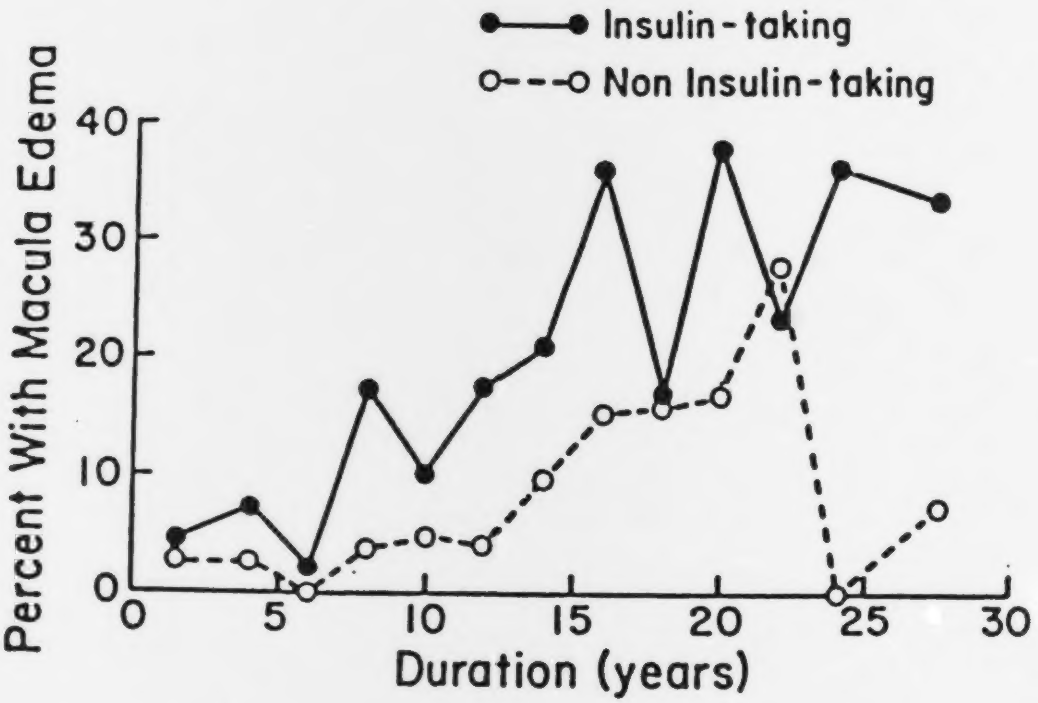
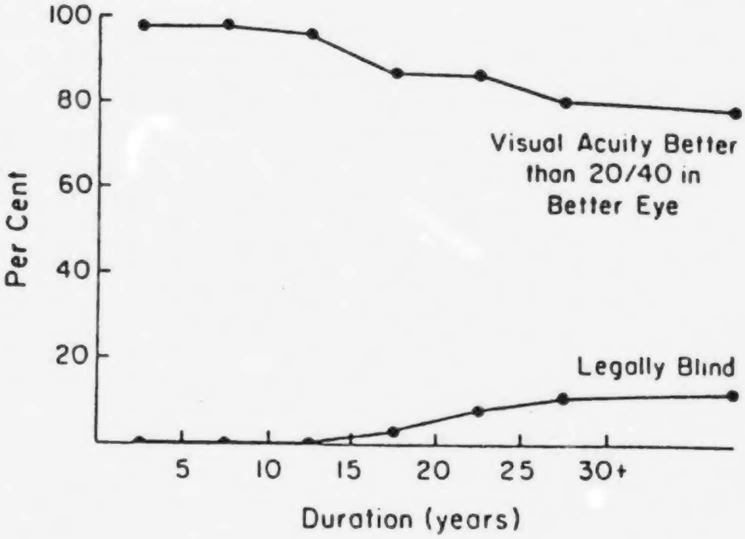


Figure 4. The frequency of macular edema by duration of diabetes for insulin - and noninsulin-taking older onset persons.

Figure 5



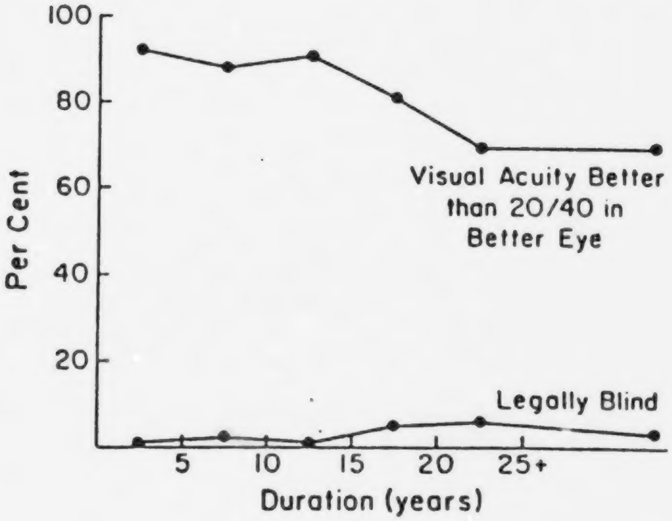


Figure 5a. Percent of younger onset diabetic persons with visual acuity of 20/40 or better, and of those with legal blindness by duration of diabetes.

Figure 5b. Percent of older onset diabetic persons with visual acuity of 20/40 or better, and of those with legal blindness by duration of diabetes.

Although no Canadian population based study is available, voluntary reporting by ophthalmologists to the Canadian National Institute for the Blind (CNIB) provides an estimate of the common causes of blindness in Canada in the various age groups (Table 3). Diabetes accounts for 10% of all blindness (7). In the age group of 20-64 years, diabetes is the cause of approximately 30-54% of blindness, with a mean of 45%. This is a significant cause of blindness in the most productive age group. The economic loss to these individuals during that period may be an astounding burden on society.

Diabetic Eye Care In Canada

The state of ophthalmic care in Canada cannot be extracted through the scientific method of individual population-based studies (8,9). The information is ascertained from anecdotal accounts obtained through telephone interviews with ophthalmologists across Canada who spend a large portion of their time treating diabetic retinopathy. They span the entire country from Vancouver to Newfoundland.

Throughout the discussions with these colleagues there appears to be great heterogeneity in the ophthalmic care in diabetic patients across Canada. The reasons for this are many. Firstly, Canada is a large country geographically, with a few areas of concentrated population representing major centres. The accessibility to a large treatment center may be very difficult. The many different regions of Canada are often afflicted with poor climate in which during the long winter months travel to these large centers may be difficult. The cost of travel is often entirely at the expense of the patient.

The largest contrast may be seen in the provinces of British Columbia and Newfoundland. Dr. Gordon Harris of the University of British Columbia, Vancouver, and Dr. Val Conway of the Health Science Center of St. John's, Newfoundland provided pertinent information on the general diabetic health care in these two regions.

Southwestern British Columbia has a very favourable climate. This attracts many doctors to this area. There are 5 retinal specialists in the Vancouver area and 2 in Victoria. They are not over-burdened with service. The communities tend to send most of their diabetic problems to these major centers. There are only one or two centers in which there are lasers run by general ophthalmologists, but usually, they too send their patients to the major center. Annually, there are province-wide meetings in which the attendances are excellent. There are frequent up-dates on diabetics retinopathy. This is what Dr. Gordon Harris feels is the key to successful general primary care of diabetic eyes. All in all, he has been quite happy with the state of the art in British Columbia.

Table 3

THE MOST COMMON CAUSES OF BLINDNESS BY AGE GROUP CASES REGISTERED AS BLIND DURING 1972

Age Group	Retrolental Fibroplasia	Cataract	Glaucoma	Myopia	Retinitis Pigmentosa	Optic Nerve Atrophy	Uveitis Choroiditis	Retinal Detachment	Macular Degeneration	Albinism	Nystagmus	Diabetic Retinopathy	Injuries Poisonings	Multiple Sclerosis
5 & Under	11	20	0	1	0	10	1	0	1	5	3	0	9	0
6 - 15	1	17	0	10	9	14	3	2	4	14	25	0	3	0
16 - 19	0	4	1	3	4	10	0	0	2	5	3	0	8	0
20 - 29	3	3	0	4	18	8	2	2	6	4	5	25	9	3
30 - 39	0	7	3	9	10	5	1	3	7	0	1	24	7	7
40 - 49	0	0	3	8	12	7	4	2	8	1	1	16	9	5
50 - 64	1	14	34	16	13	17	3	11	32	0	0	77	10	4
65 - 80	0	34	103	14	11	13	5	8	243	0	1	68	5	0
81 & Over	0	54	72	7	3	3	6	4	310	0	0	6	1	0
TOTALS	16 0.7%	153 7.1%	216 10%	72 3.3%	80 3.7%	87 4.0%	25 1.2%	32 1.5%	613 28.3%	29 1.3%	39 1.8%	216 10%	61 2.8%	19 0.9%

In contrast, Dr. Val Conway of St. John's, Newfoundland reports that general diabetic eye care has been unsatisfactory in his province. There are approximately 5 and occasionally 6 ophthalmologists on the island providing general ophthalmic care. Although he and Dr. Gordon Johnson are the main retinal specialists, the service aspect is not adequately covered by the manpower. Consequently, because of their over-burdened practices, there is no time for educational symposia. What he fears also is the fact that referrals attracted by educational symposia cannot be serviced. It may be important for manpower to look at the distribution of ophthalmologists and the areas which are not particularly attractive for the doctors should have a better economical incentive.

Dr. Val Conway also feels his main obstacle is that the general practitioners are not educated enough in the care of diabetic retinopathy and some of the risk factors involved. Again this goes back to education of the primary care doctor and also to the availability of the service. He is happy that Dr. Ed Collins, who recently trained in Halifax, is starting up another retinal center in Gander. As many of these patients come from remote areas and are very reluctant to travel, it may be better to establish centers which are not too removed from the patients themselves. Dr. Val Conway also observed that some of the general ophthalmologists who have been out in practice for many years tend not to refer patients for secondary or tertiary care.

Dr. Anne Hoskins of Dalhousie University, Halifax echoes the thoughts of Dr. Val Conway. She feels the root of the problem may stem from the lack of ophthalmological teaching at the undergraduate level. Again, the refresher courses are well-received by the general ophthalmologists and may be the key to better management.

Dr. Julius Gomolin of Montreal, who sees an urban population, notes that the general ophthalmologists tend to refer much too late, and referrals from endocrinologists tend to be very early. He also observed that the ophthalmologists who have been trained in the last 5 years are much more informed about when to refer diabetic patients and what the indications for laser photocoagulation are. Dr. Gomolin has done various continuing education series, specifically for general practitioners. Many months following each symposium, there has been a surge in the ophthalmic referrals for diabetic eye examinations. Many of the rural referrals go to Quebec City and Sherbrooke. The Eastern Townships themselves are being serviced adequately with primary care.

Drs. Michael Shea and Lionel Chisholm of the University of Toronto also see a heterogeneity in the care of the patients referred to them. All of the above factors are found to be important.

Levels of Intervention

The use of photocoagulation to treat proliferative diabetic retinopathy has gained wide-spread acceptance in ophthalmic practice since its introduction in 1959 by Meyer-Schwickerath (10). However, no controlled clinical trial was started until the Diabetic Retinopathy Study (DRS) was begun under the sponsorship of National Eye Institute (NEI) in 1971 (11). This randomized, controlled, clinical trial involved more than 1700 patients enrolled in 15 medical centers. Strong emphasis was placed on the completeness of follow-up with minimal bias and assessment using good stereo fundus photographs of the retina. The accumulating data were also periodically reviewed by the Data Monitoring Committee.

By 1976 the preliminary report on effects of photocoagulation therapy was reported by this group. After 2 years of following treatment, there was a definite beneficial effect of photocoagulation on reducing severe visual loss in the treated eye as compared to the untreated eye (12). As a result, all patients in the early study were informed of the results and when possible, the initially untreated eye was also given treatment. A publication in January 1978 (13) further confirmed the reduced rate of development of severe visual loss as well as some of the side-effects of laser treatment such as loss of visual acuity and constriction of peripheral field. The risk of these harmful side-effects was considered negligible in eyes with retinopathy in moderate or severe proliferative disease where the risk of severe visual loss without treatment was great.

In the DRS study, the four risk factors were identified as indicators of possible severe visual loss and diabetic retinopathy (14). The four risk factors are:

1. Presence of vitreous or preretinal hemorrhage.
2. Presence of new vessels.
3. Location of new vessels on or near the disc.
4. Severity of new vessels.

The two-year incidence rate of severe visual loss in untreated eyes is grouped according to the number of risk factors. Several points are noteworthy: 1) The risk of visual loss rises progressively as more risk factors are added, 2) the risk remains moderately low with one or two risk factors and then jumps from 8.5% to 26.0% as the number of risk factors increases from 2 to 3, 3) the eyes previously described as having high-risk characteristics now can be seen with 3 or more risk factors. It is for the untreated eyes with 3 or more of these risk factors that the DRS protocol was changed in 1976 for consideration for treatment. Thus, a useful rule of thumb is that eyes having 3 or more risk factors are at high risk. For these eyes at "high-risk" of severe visual loss there is an absolute indication for photocoagulation.

For the eyes with severe non-proliferative retinopathy or preproliferative retinopathy or those with proliferative retinopathy without high-risk characteristics, prompt laser photocoagulation is attractive. With treatment, the 12%, 2 year risk of severe visual loss observed in the high-risk group occuring even with photocoagulation might be avoided. On the other hand, postponing of photocoagulation until high-risk characteristics develop defers the risk of photocoagulation. Eyes followed and treated as soon as high-risk characteristics develop might be expected to do better than the DRS high-risk group which included eyes which already had severe retinopathy at the time of treatment.

DRS findings do not provide a clear choice of prompt photocoagulation or deferral in this group of patients with severe non-proliferative disease or proliferative disease without high-risk characteristics (15). These questions will be addressed by another randomized, clinical trial, the Early Treatment of Diabetic Retinopathy Study (ETDRS) (16). Thus far, clear indications have been provided by the DRS for patients with retinopathy with high-risk characteristics.

The other modality of treatment is vitrectomy which has been highly perfected by leading investigators in this field. However, the role of vitrectomy in diabetic retinopathy treatment is still unclear. Presently, there is a Diabetic Retinopathy Vitrectomy Study (DRVS) (17) which is evaluating the role of this intervention in a randomized, clinical trial.

The principle of the DRVS is to examine two groups of patients. One has a recent vitreous hemorrhage and the second group has severe fibrovascular proliferation without severe vitreous hemorrhage. The patients are allocated randomly to either prompt vitrectomy or deferral for one year. The second group with severe fibrovascular proliferation in the absence of severe vitreous hemorrhage is observed with no treatment to see if early or late vitrectomy should be done eventually. This was based on observation in 6 clinics in which the results were pooled together in a retrospective manner. Forty-one percent of 140 eyes with vision of less than 5/200 and in which vitreous hemorrhage has been present for a year or more had achieved visual acuity of 20/200 or better 4-9 months after vitrectomy. There are no control data available naturally. However, a group of patients of 58 eyes, with visual acuity of less than 20/200 and vitreous hemorrhage severe enough to preclude any observation of fundus had a recovery rate to 20/200 or better after one year; without treatment the recovery rate was only 8%. This provided the impetus for this randomized trial. There have been no published conclusions on the results of this study. The results are expected to be published in the very near future.

Other ocular diseases such as glaucoma and cataracts are found to be more common in the diabetic patients; these can be readily recognized and treated by general opthalmologists. Thus vigilant ocular examinations will not only detect diabetic retinopathy, but also treat other causes of blindness common in the older age group.

Recommendations for Ophthalmic Care

The following are recommendations as to when the patient should be seen and who should be evaluating diabetic retinopathy based upon the epidemiological studies. The ability of the internist, general ophthalmologist, and retinal ophthalmologist to diagnosis proliferative retinopathy was examined at the University of Pennsylvania (8). This was performed under optimal conditions. Twenty-three physicians performed retinal examinations on 10 diabetic patients and 1 normal patient. The team consisted of 10 internists, 2 diabetologists, 4 senior medical residents, 4 general ophthalmologists and 3 retinal specialists. On the basis of 7 view stereo fundus photographs the diagnoses were confirmed initially. The patients were instructed not to provide any clinical data. All the eye examinations done with dilatation were performed independently without any time limit. In this group of patients there were 7 eyes with the proliferative diabetic retinopathy. Other diagnoses include normal examination and other eye findings representative of common types of diabetic retinal disease.

A serious error was considered to occur when the diagnosis of proliferative diabetic retinopathy was missed. Internists missed 52% of the diagnoses of proliferative retinopathy. The medical residents missed 50%, diabetologists missed 33% and general ophthalmologists missed 9% while retinal specialists did not miss any. The diagnosis was correctly determined by the physical examiners in 39% of the examinations. The internists, senior medical residents and diabetologists had correct diagnosis rates of 27% , 31% and 36% respectively. General ophthalmologists and retinal specialists had correct diagnosis rates of 52% to more than 70% respectively. This was an important study which points towards the fact that ophthalmologists should be screening diabetic patients because untreated proliferative retinopathy can cause severe visual impairment. What is more important is the fact that the patients who have disease should be screened and treated appropriately.

The other disturbing factor of this study is the fact that even retinal specialists were only able to have an accurate diagnosis in 70% of all cases. As a result, it has been recommended that ophthalmologists confirm the diagnosis when they suspect the clinical diagnosis by using retinal photography or fluorescein angiography, as these are proven to be very important adjunctive diagnostic procedures in the treatment of diabetic retinopathy.

Another important aspect of treatment is the dissemination of new medical information to ensure that the physicians involved are aware of certain successful results. Two years after the results of the DRS were published only 35% of all physicians were aware of it, although each cared for more than 50 diabetic patients in his practice (9). Fifty-six percent of the physicians thought that insulin-dependent diabetes should be routinely evaluated by an ophthalmologist. These data suggest that there is a serious deficiency in the provision of eye care for diabetic patients.

This leads to the very important aspect of care for the patients of all diseases, the need to hold updates on diseases. These symposia should be readily available to the physicians from even the most remote part of the country. They can appear in the form of what recently has been a successful run of medical programs such as Eye Stat which are video tapes of programs from prominent investigators. The other alternative is to ensure that new information is presented at major meetings such as that of the Canadian Ophthalmological Society. Not only do physicians require education, but also other paramedical workers and the patients themselves would benefit from educational programs.

Ideally, for each center in which a large population of diabetics are being treated, various pamphlets should be available explaining the possible complications such as diabetic retinopathy. These should be informative without being intimidating. The process should be explained in lay terms pointing out the dangers such as proliferative disease and macular edema. It would be useful to explain to patients about the process of retinal photography and also fluorescein angiogram. The side-effects from fluorescein such as, the yellowing of the skin and the yellowing of the urine should be described. The principle behind doing these exams should also be given.

Patients should be informed that they may be asymptomatic, and yet have lesions requiring photocoagulation. The discomfort and side-effects of laser photocoagulation should also be well described in this pamphlet.

I personally have spoken to diabetic patients in large diabetic organizations. There is a large interest either on the part of the relatives or of the patients themselves. These sorts of patient education symposia should be encouraged.

A set of guidelines describing when the patients should be examined by a retinal specialist may be useful to both physicians and to the general ophthalmologists treating diabetics. According to the Wisconsin Epidemiological Study, the data indicates that careful ophthalmic evaluation is a very important aspect of the medical treatment of diabetic patients. For young-onset, insulin-taking diabetics routine examinations should begin no later than the fifth year after diagnosis, and frequency of examination should be determined by the severity of the retinopathy. The increased frequency of proliferative retinopathy after 10 years of diabetes and the difficulty in detecting proliferative changes by non-ophthalmologists (8) add an impetus to the need for frequent and careful ophthlamic examination. During this period of time general ophthalmologists should refer the patient to a retinal center where fluorescein angiography and fundus photography can be performed.

In the group of older age onset of diabetes (when the diagnosis is made at the age of 30 or more) (2), proliferative retinopathy can be seen in 2.0% of patients with diabetes of less than 5 years. This certainly makes it very important that the older onset patients should have an ophthalmic examination even at the time of diagnosis. The time of diagnosis does not reflect the clinical onset of disease and thus many of these patients may have retinal disease at the time of diagnosis. Macular edema was found to be present in 3% of these older onset patients during the first three years of diabetes with later increase up to 28% over 25 years or more. Thus, again it emphasizes the need to have early ophthalmic evaluations on this group of patients.

Future Research Issues

The future purpose of research in diabetic retinopathy is two-fold. One is to advance treatment of diabetic retinopathy with a clinical randomized trial. The second is to look at the prevention of the disease, in particular, in association with long-term diabetic control.

As mentioned, in the clinical evaluation of the timing of treatment of patients with severe non-proliferative diabetic retinopathy or proliferative retinopathy without high-risk characteristics important questions remain unanswered. Is early photocoagulation preferable to deferral? Is extensive scattered treatment in DRS necessary, or might less extensive treatment retard the progression of retinopathy and be attended by fewer harmful effects? Apart from its value in treating the proliferative features of diabetic retinopathy, what is the role of photocoagulation in diabetic maculopathy? Could low doses of Aspirin possibly slow the progression of retinopathy? These are all questions being addressed by the controlled clinical trial, the Early Treatment Diabetic Retinopathy Study (ETDRS). No conclusions have been announced by the Data Monitoring Committee and the study group.

Macular edema is a very significant aspect of visual impairment in both the younger onset and older onset diabetic patients. This has been noted by the Wisconsin Study (4,6). The treatment of macular edema has been studied byvarious investigators in the past (17,18,19). These have usually been clinical accounts. However, there has been a randomized clinical trial performed by the British Multicenter Study Group using xenon laser photocoagulation which was found to be effective (20). The ETDRS (16) as mentioned previously, has not concluded its findings on efficacy of treatment with argon laser photocoagulation.

Experimental models using laser photocoagulation, both the krypton and the argon, have shown interesting results (21). Dr. John Marshall at the Institute of Ophthalmology in London has noted that krypton laser in particular causes the retinal capillaries endothelial cells to divide over the areas of laser exposure. It also seems to extend in an area well away from the lesions of the laser. The stimulation for cellular replication within the interretinal vasculature may be responsible for tissue destruction in the deeper layers performed by the laser and may be very important in the resolution of the macular edema. Presently, there is a proposed project determining the efficacy of the argon blue-green versus the krypton in the treatment of diabetic macular edema (22).

Another interesting concept which the University of Toronto may be examining is the role of good diabetic control during laser photocoagulation and its effects on the final treatment results. There have been anecdotal reports of exacerbation of the diabetic retinopathy with good diabetic control. No study has examined the role of the tight control during the period of photocoagulation to compare that to a group with moderate control.

Pituitary ablations were once in vogue as a form of treatment for diabetic retinopathy. With the high morbidity and mortality associated with this procedure, and with the advent of effective photocoagulation, pituitary ablation is no longer favoured. Growth hormone was strongly implicated in the success of pituitary ablation in retarding diabetic retinopathy.

Young diabetic patients have a "protective" effect in the prepubescent period with very little retinopathy evident. This "protective" effect is lostat puberty. Secretion of growth hormone and other changes following puberty have been suggested by the absence of retinopathy in hypo-insulinemic, hyperglycemic, diabetic dwarfs (23). This has led a group of investigators at the University of Toronto to design a study in which a somatostatin analog for the treatment of acromegaly will be used to treat a selected group of patients with diabetic retinopathy.

Aldose reductase is an enzyme found in lens epithelium and endothelial pericytes. In the presence of high blood glucose levels, the sugar is converted to an alcohol, sorbitol. Sorbitol does not cross cell membranes and is known to cause an infusion of water resulting in cataracts. Damage to the pericytes may be the result of a similar process. Pfeiser has recently started a study in which sorbinol, an aldose reductase inhibitor is evaluated in the light of its role in the prevention of microvascular complications.

Despite all the efforts of the clinical trials on the treatment of diabetic retinopathy, the key probably lies in the study of the relationship of diabetic control to diabetic retinopathy. At the University of Pittsburg (24), a study was performed to determine the relationship between the levels of long-term antecedent diabetic control in early diabetic retinopathy changes. This was performed in insulin-dependent diabetics of age 14-17 years of age with a duration of at least 8 years of diabetes. The glycosylated hemoglobins which were measured over a period of 3.1 years were correlated between degree of metabolic control as measured by glycosylated hemoglobin and the presence of early diabetic retinopathy defined by angiography. This was a well designed, carefully conducted study, but it does not prove the relationship to be one of cause and effect.

The NEI have sponsored another diabetic study in which this very question is being addressed. This is the Diabetes Control and Complication Trial (DCCt) (25). Specifically, the relationship between control of blood glucose and the development of early vascular complications is evaluated. In the past this study would not have been feasible because of the lack of the ability to produce tight control. Now with the use of insulin pumps the experimentaldesign is possible. Patients in the control group are given standard therapy in which no more than 2 injections of insulin daily are given. The experimental group will have an insulin pump along with frequent self-blood-glucose monitoring to strive to maintain hemoglobin A/C levels within two standard deviations of the mean for the non-diabetic population. This clinical trial is just beginning and it will be a few more years before any conclusions may be drawn from this study.

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DIABETIC NEPHROPATHY

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Background

End Stage renal failure (ESRF) due to progressive glomerulosclerosis occurs in more than 40% of patients with type 1 diabetes (1,2). By the time the disease is clinically recognized by the appearance of proteinuria and rising serum creatinine, the glomerular capillary damage is advanced and probably irreversible. In general, clinical nephropathy is evident at a mean duration of 17 years following the onset of insulin dependent diabetes; ninety percent of cases will progress to ESRF within 7 years (3). The single most important factor in preventing a more rapid decline in renal function once glomerular filtration is impaired, is aggressive blood pressure control (4). There is presently no evidence from controlled trials that strict blood sugar control will prevent the relentless progression of advanced diabetic glomerulosclerosis to ESRF (5).

How does one recognize the diabetic patient who will develop progressive nephropathy? There is good evidence that a persistent increase in the urinary excretion rate of albumin in the range of 30 to 150 ug/min (normal 30 ug/min), enhanced by exercise, predicts those patients who are at risk for developing progressive disease (6). A 14 year longitudinal study by Viberti et al (7) revealed that the risk of type 1 diabetic patients for developing clinical nephropathy (Albustix positive proteinuria) was 24 times greater in patients with elevated microalbuminuria compared to those with a normal excretion rate.

There is increasing, but no definitive evidence in man, that near normal blood glucose control acutely reverses this abnormal elevation of microalbuminuria. The Steno Study Group (Steno Memorial Hospital, Gentofte, Denmark) analyzed the effect of two years near normalization of blood glucose on GFR and urinary albumin excretion rate in 29 insulin-dependent diabetic patients, randomly allocated either to unchanged conventional treatment (UCT, N=13) or to continuous subcutaneous insulin infusion (CSII, N=16) (19). All the patients had Albustix negative urine and normal serum creatinine and arterial blood pressure. However, only 3 out of the 16 CSII patients started with abnormally increased microalbuminuria, whereas 5 out of 13 of the UCT patients initially had increased microalbuminuria. Comparing the two groups, there was a trend towards increasing microalbuminuria in the UCT group. However, due to the small numbers and different stages of nephropathy at the outset of the study, no definite conclusion could be drawn about the effect of near normalization of blood glucose and prevention of progressive nephropathy. The study did demonstrate that the state of glomerular hyperfiltration can be reduced and frequently normalized during prolonged near normalization of blood glucose levels. The result of reversing the state of glomerular hyperfiltration on the progression of nephropathy remains to be investigated.

The Kroc Collaborative Study Group recently published the results of a multicentre randomized trial to determine both the feasibility of maintaining blood glucose control on diabetic microangiopathy and albuminuria (10). Nearnormalization was achieved in 35 insulin-dependent patients using CSII for 8 months in contrast to the 35 patients on conventional insulin treatment who had persistent hyperglycemia. In this study, 10 patients in each treatment group had elevated microalbumin at the onset. With CSII there was a progressive and significant decline in microalbumin to a normal range. In contrast, the urinary albumin excretion rates in the conventionally treated group remained unchanged. Unfortunately, glomerular filtration rates were not reported in this study.

In summary, long-term near normalization of blood glucose may prevent progression of diabetic glomerulosclerosis, though further prospective randomized trials with larger subject numbers are required to answer the question definitively.

It is well established in the streptozotocin diabetic rat model that the earliest functional change i.e. glomerular hyperfiltration and structural alterations (increased glomerular basement membrane and mesangial matrix) are normalized with strict blood glucose control (11). However, the cause and effect relationship between hyperglycemia and development of increased microalbuminuria denoting progressive glomerulosclerosis in man or animal models remains to be proven.

Medical Impact of Diabetic Nephropathy in Canada

The number of new ESRF patients with diabetic nephropathy entering dialysis and transplant programs across Canada increased from 65 (9% of total) to 222 (17% of total) patients between 1976 and 1983 (12). In general, 10-25% of the patients on dialysis in Canadian centres are diabetic. It is now the second most common cause (following primary glomerulonephritis) of ESRF (13).

The cost of treating diabetics with ESRF in Canada is substantial and will continue to increase unless this complication is prevented.

EARLY PROGRESSIVE DIABETIC NEPHROPATHY

Recognition

Presently, the earliest clinical marker of progressive diabetic glomerulosclerosis in man, short of repeated renal biopsies, is a persistent increase in microalbuminuria (equal to or greater than 30 ug/min). This level of microalbuminuria is not detectable by Albustix which measures trace protein 143 ug/ml + 51 ug/ml SD or by routine 24-hour urine protein determination. The analysis of microquantities of albumin in the urine requires a specific radioimmunoassay or more accurately an enzyme-linked immunosorbant assay (ELISA) method. Both of these methods utilize anti-human albumin antibodies to detect small quantities of albumin.

Management

With our present knowledge, the ideal way to attempt to prevent or reverse the earliest glomerular changes leading to progressive nephropathy is to achieve near normalization of blood glucose levels. All new diabetic patients then should have yearly documentation of the urinary excretion of albumin. If the level progressively increases, even within the normal range, a standardized exercise test could be used to enhance an abnormal rise in microalbuminuria, perhaps more sensitive marker of advancing disease. The identification of increased risk of developing progressive nephropathy would provide the incentive to both patient and physician for achieving the best possible glucose control. Hypertension, if present, should also be strictly controlled (diastolic equal to or greater than 90 mmHg).

Normalization of HbA_1 levels and reversal of microalbuminuria to a normal range would signify successful management. In the event that HbA_1 levels normalized but the increased microalbuminuria progressed, a closed renal biopsy would be indicated to rule out the presence of another type of primary or secondary glomerular lesion.

Presently, the early management of patients without clinical nephropathy is exclusively in the hands of the endocrinologist and general internist. Renal function is followed with serum urea, creatinine and 24-hour creatinine clearance and total urine protein. I am unaware of any centre in Canada that is measuring urinary excretion rates of microquantities of albumin.

Though many diabetics in Canada are now utilizing home glucose monitoring and optimizing glucose control, patients that may be at increased risk for development of diabetic nephropathy are not being preselected for such intensive programs. Several questions are presently in the mind of nephrologists and endocrinologists about this dilemma. Can patients realistically achieve near normalization of blood glucose with present methods of home glucose monitoring and constant insulin infusion without the major risk of recurrent hypoglycemia? If this degree of blood glucose control were achieved and maintained for years would it ensure that diabetic nephropathy would be reversed or prevented in the early stages?

ADVANCED DIABETIC NEPHROPATHY

Ideal Management

Type 2 diabetic patients develop clinically apparent nephropathy in the third and fourth decade of life. At this time, they are often pursuing an education, a new career and marriage. Within a few short years, most of these patients are confronted with the psychological, social and emotional problems of dialysis and transplantation. As well, progressive uremia itself accelerates all the major complications of diabetes e.g. hypertension, retinopathy and neuropathy.

There are three major factors in the ideal management of advanced diabetic nephropathy. First, the patient must be given an optimal chance to cope with this relentlessly progressive disease. The patient and family can realistically plan for the future if they are aware of the progressive nature of diabetic nephropathy. This can be a gradual process in which the patient and family are slowly introduced to the concept of treating ESRF. With the aid of the renal team i.e. physician, renal services coordinator, social worker, the transition period from clinical nephropathy to successful treatment of ESRF can be as atraumatic as possible.

Second, since it is well documented that hypertension accelerates glomerulosclerosis, blood pressure should be rigorously controlled. The patient should also be aware of the consequences of elevated blood pressure, and play an active role in its management, for instance, in home blood pressure monitoring. Finally, the patient advancing toward end stage renal failure should be considered for early transplantation, preferably from a nondiabetic living related donor, with or without a period of dialysis.

Though optimal glucose control is always desirable, there is no positive evidence that progression to ESRF will be avoided with improved glucose control. However, once the patient has received a renal transplant, recurrence of diabetic glomerulosclerosis may be delayed or avoided with strict glucose control (14, 15).

Clearly, there is a role for the nephrologist once clinical diabetic nephropathy is apparent. The nephrologist is more familiar with the ESRF programs available to the patient. Discussion of renal transplantation should be started well in advance of ESRF. This allows both the patient and family to have time to discuss and decide about living related kidney donation. As uremia progresses, the diabetic often becomes more debilitated than other patients with ESRF because of other diabetic complications such as retinopathy and neuropathy. Early dialysis may prevent the uremic component of these complications, provide easier management of hypertension and allow the patient to continue as many normal activities of daily living as possible. As well, early home dialysis training is more successful when the patient is physically well and psychologically and emotionally prepared. Waiting till the patient is in the last throes of ESRF provides no advantage.

Along with the help of the endocrinologist optimal glucose management should be achieved, particularly following transplantation.

Present Management of Advanced Diabetic Nephropathy in Canada

When invited to attend this workshop, I initiated a survey of the Divisions of Nephrology across Canada with regard to the present and future management of diabetic nephropathy patients. As of April 24, 1985, 15 out of 24 responses were received. The following summarizes these results.

The management of diabetic patients with clinical nephropathy before ESRF ensues is equally divided between endocrinologists and nephrologists. One-third are followed exclusively by an endocrinologist, one-third only by a nephrologist only, and one-third by both.

In the majority of centres 10-25% of the ESRF population is composed of diabetics though in 3 out of 15 centres this percentage is between 25 to 50%. However most centres, 13 out of 15, did not have a special clinic or clinical practice designated for the management of diabetic nephropathy.

The belief that a specialized clinical setting (e.g. combined management of a nephrologist, endocrinologist, ophthalmologist, dietitian, nurse clinican, etc.) would be advantageous for the treatment of diabetic nephropathy patients compared to a general nephrology clinic or office practice, was equally divided. In general, the Directors or representatives of the smaller centres e.g. St. John's, Newfoundland, stated that patients with diabetic nephropathy were too few in number to warrant a specialized clinical setting. However, the opposite was true for the larger centres e.g. Toronto General Hospital, where the number of diabetic nephropathy patients is substantial. In the few centres where a specialized clinic is presently functioning e.g. Health Science Centre, Winnipeg, Manitoba, it is believed that "the availability of the interdisciplinary approach is very useful, particularly for out of town patients who make up to 50% of the outpatient diabetic nephropathy population".

There was a consensus among the nephrologists that once in ESRF programs, diabetics presently receive optimal treatment. Though the survival figures for large numbers of diabetic patients in dialysis and transplantation programs compared to nondiabetics are not available from across Canada - the following information is available from the United States.

Table 1
U.S. Comparative Survival Of Diabetic Versus Non-Diabetic ESRD Patients (16)
1977-1980

Patient Category	N	Percent Patient Survival	
		1 Year	3 Years
DIABETIC			
Dialysis	5856	75	39
Cadaver Transplant	518	79	65
Live Related Transplant	268	89	82
NON-DIABETIC			
Dialysis	15560	87	68
Cadaver Transplant	2646	86	80
Live Related Transplant	1045	96	91

Patients in Table 1 were not matched for demographic characteristics, risk factors (e.g. hypertension or ischemic heart disease), or centres. It has recently been shown that the survival of adults with ESRF depends on age, the presence of left sided heart failure, duration of diabetes (17) and elevated diastolic blood pressure (18). That is diabetic nephropathy itself is not an added risk factor (greater than other causes of ESRF). I believe that future, risk matched studies will probably show that patients with diabetic nephropathy have no substantially greater risk than the general ESRF population.

Table 1 does indicate that diabetic ESRF patients treated by transplantation have a better short and long-term survival than those treated with dialysis. Early transplantation, preferably with a living-related donor, is the present treatment of choice.

Conclusions

1. Strict glucose control (ideally normalization) in the earliest stages of progressive diabetic nephropathy is the only known intervention that may reverse or prevent the disease.

2. The earliest stages of progressive nephropathy characterized by persistently elevated microalbuminuria, exacerbated by exercise, is not being recognized in Canadian centres. Therefore, aggressive intervention with strict glucose control is occurring too late.

3. The techniques for accurately determining microquantities of albumin in the urine are presently not established or if available in Canadian centres are not being utilized in clinical practice.

4. Management of established diabetic nephropathy should include an explanation to the patient of inevitable progress to ESRF, normalization of blood pressure and planning for early dialysis and preferably living related-donor renal transplantation. In Canada, not all diabetics with nephropathy are presently referred early enough to the nephrologist for optimal management of ESRF.

5. Clinical investigation of the early stages of diabetic nephropathy by nephrologists is presently lacking in Canada.

Recommendations

Note: The following includes a number of suggestions made by Nephrology Division Directors in a recent Canada wide survey about the management of diabetic nephropathy.

1. The usefulness of elevated microalbuminuria as a marker of early progressive diabetic nephropathy and the reversibility of this condition with strict glucose control should be established in Canada. This would require:

    (a) A multicentre controlled trial or individual large centre (Toronto or Montreal) trials over 3-5 years.

    (b) The establishment of standardized assays (radioimmunoassay or ELISA methods) to determine microquantities of albumin in the urine in centres across Canada.

    (c) Dedicated clinical investigators - endocrinologists, nephrologists and other trained personnel (dietitians, nurse clinicians) to optimally control blood glucose levels of patients who may have preventable or reversible renal lesions. (This management would be greatly aided by improved methods of glucose monitoring and insulin delivery ?computerized?)

Similar larger controlled trials will be taking place throughout the United States (N.I.H.) and Western Europe over the next 5-10 years. By establishing the laboratory technology and clinical expertise during this clinical investigation period, Canadians will be capable of entering a new era of prevention without delay.

2. Once diabetic glomerulosclerosis is established with significant proteinuria (equal to or greater than 300 mg/day) and/or serum creatinine begins to fall, the nephrologist should begin to follow the patient jointly with the attending endocrinologist or

internist. As the disease progresses, the care of the patient should fall more into the hands of the nephrologist to ensure optimal early management of ESRF. This includes:

(a) Optimal blood pressure control

(b) Early dialysis to prevent added uremic complications e.g. worsening neuropathy and retinopathy.

(c) Consideration for early renal transplantation and an active search for suitable non-diabetic living-related donors.

3. The Divisions of Nephrology across Canada should take a more active role in establishing specialized clinical settings for the management of diabetic nephropathy. This would include outpatient clinics, or, in smaller centres, individual practices in which a nephrologist, endocrinologist, dietitian, nurse clinican, etc. would participate in the ongoing treatment of diabetic nephropathy patients. Not only would this provide uniform and optimal management of patients with diabetic nephropathy, it would also facilitate the clinical investigation of the condition.

4. The pathophysiological mechanisms of early progressive diabetic glomerulosclerosis should be pursued by Canadian scientists using animal models. If the link between increased microalbuminuria, progressive disease and reversibility with improved glucose control were known, perhaps other means of prevention may evolve.

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DIABETIC NEUROPATHY

Vera Bril, M.D.

Neuropathy is a frequent and well-known complication of diabetes mellitus described in the last century. In spite of this early recognition, controversies persist as to its prevalence, significance, etiology and therapy. Much of the information in this report is derived from the world literature as studies addressing these issues have not been undertaken in Canada.

Prevalence

A central issue concerns the way in which neuropathy is identified. This determines the prevalence of neuropathy in the diabetic population. Symptomatic neuropathy is reported as existing in 2 to 10% of diabetics (31, 197, 141, 17, 26). If we then include those with asymptomatic clinical neuropathy, the rate increases to at least 20 or 30% (17,55). However, if we subsequently extend our clinical examination with electrophysiological testing, the rate increases to as many as 75% of all diabetics (26, 152, 98, 112, 90). Finally, if we proceed to biopsy of the sural nerve or even the dermal nerves, as many as 80 to 100% of diabetics show abnormalities (85, 46). The increasing prevalence of neuropathy in the diabetic population as a function of method of detection is shown in Figure 1. Graphically we observe that intensive study of the diabetic population elicits increasing numbers with neuropathy. As physicians we are most concerned with severe cases requiring therapy, although as scientists, we are concerned with development of this complication in the entire population. Furthermore the incidence of abnormality increases with increasing duration of diabetes mellitus, so that an initial figure of 10% at diagnosis of diabetes becomes 50% after 25 years (107).

Assuming one million diabetics in Canada, we therefore acknowledge that 200,000 have clinical neuropathy and of these, about 8,000-10,000 have severe forms of neuropathy. Additionally, with time the numbers affected increase. These numbers include all forms of diabetic neuropathy.

Figure 1

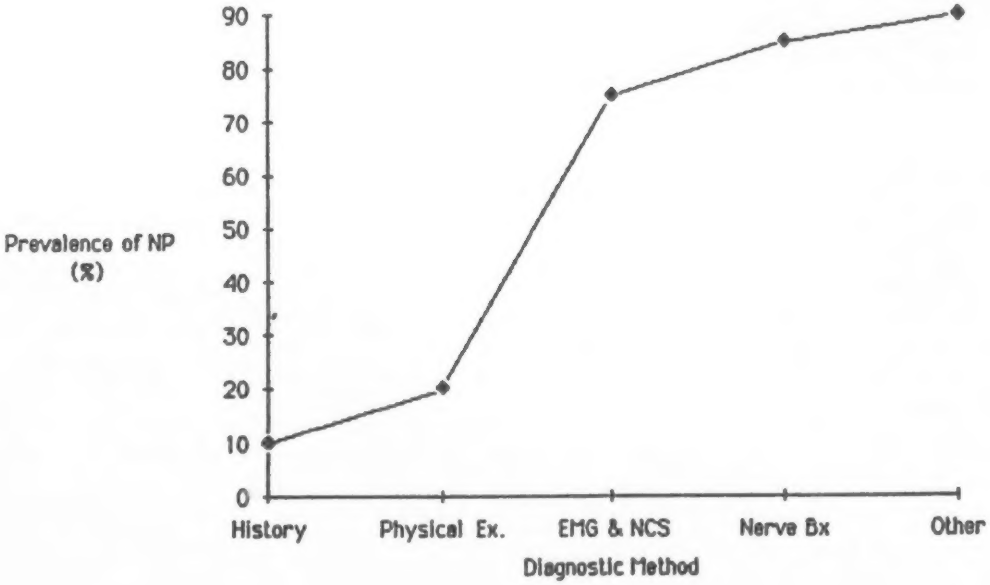

Figure 1. Prevalence of neuropathy in the diabetic population as a function of method of detection.

What is the significance of this high prevalence? We must treat the 10,000 people who are severely affected. We must find out why they become affected and we must try to prevent the evolution of this complication which might be easier if we knew how it comes about.

Clinical Presentation

Most patients with diabetic neuropathy have a spectrum of abnormalities, but several distinct clinical pictures emerge. Classifications are based on these differences, for example, that of Brown and Asbury (24), or Thomas (134). Patients often present with one clinical syndrome, eg. painful mononeuropathy, and have evidence of others on examination. Therefore I think that a limited clinical classification similar to that suggested by Thomas (134) is useful (Table 1).

Table 1

1. **Peripheral Sensorimotor Neuropathy**
   - autonomic neuropathy (less than 1%)

2. **Single/Multiple Mononeuropathy**
   - cranial nerve palsies
   - truncal nerve root palsies
   - isolated peripheral nerve lesions
   - lumbosacral plexopathy

Many patients who present with a mononeuropathy have evidence of an underlying diffuse peripheral neuropathy on clinical examination even though asymptomatic for the latter. Division of the patients into these two broad categories appears justified as it is likely that different pathophysiological mechanisms underlie the development of neuropathy in each group (6, 25, 111).

The clinical presentation is highly variable. Not infrequently, patients remain asymptomatic although detailed examination (clinical and electrical) reveals clearcut evidence of neuropathy. Other patients present with acute pain and weakness and still others present insidiously.

The symptoms include pain, sensory loss, tingling, weakness, wasting, and autonomic complaints (impotence, orthostatic hypotension, diarrhoea, sweating abnormalities, hypoglycemic unawareness, and early satiety). The findings include depressed and/or absent deep tendon reflexes, peripheral glove-and-stocking sensory loss, muscle weakness and wasting, postural hypotension and postural heart rate abnormalities.

In patients with mononeuropathy, the motor and sensory symptoms are limited to the distribution of a particular nerve, or several nerves rather than being present in a diffuse and peripheral fashion.

Our major unanswered question is "Who develops disabling forms of neuropathy?".

Disabling neuropathy includes those patients with severe pain, paralysis and autonomic dysfunction.

In the last two years, we have had the opportunity to assess 164 diabetic patients with peripheral neuropathy. These patients were derived mainly from Toronto and its environs (population approximately 3,000,000). All had symptomatic neuropathy. Of these, 74% had disturbing pain and 9% were not working due to their neuropathy. Ninety-one percent had sensory symptoms, 57% had motor complaints. However, severe weakness occurred in less than 0.01%. Impotence was noted in 70% of male patients. However, other symptoms of autonomic neuropathy such as orthostatic hypotension or diabetic diarrhoea were seen in less than 0.1% of all the patients. These patients were selected to exclude those with severe nephropathy. Co-existent retinopathy was seen in 25% of our material. Ewing (53) showed that those patients with symptoms of autonomic neuropathy and abnormal autonomic function tests followed for five years had a death rate of 53%; this was due to renal failure. Some deaths were sudden and probably due to cardiac malfunction. Of those patients who had symptoms of autonomic neuropathy, but normal autonomic function tests, only 5% died over the next five years. In Pirart's longitudinal study (107), 20% developed overt peripheral neuropathy over a span of 25 years. Neuropathy developed in those with poor metabolic control over time, although more than 50% of his patients developed neuropathy with increasing duration of diabetes mellitus, in spite of efforts to achieve euglycemia. Thus, the problem of diabetic neuropathy is not insignificant from several points of view, including: numbers of patients involved, morbidity of the disorder (severe and distressing pain and/or loss of ability to work), the need for social assistance, and medical therapy. In addition, the risk of early death due to cardiac dysfunction is high in those with autonomic involvement. In most cases, the major cause of disability is pain. Only a small number have severe weakness, or life-threatening autonomic dysfunction (less than 1%). There is no method presently available to predict the patients who will develop disabling neuropathy. It is clear that a high percentage of diabetic patients will develop neuropathy with time, but not those who will develop the disabling disorder. From the studies cited it is clear that neuropathy develops more frequently in patients diabetic for longer periods of time and those exhibiting poor glycemic control for longer intervals of time. It is not clear at present how to identify those who will be most severely affected. Research in this area is required. There does not appear to be any difference in acetylator status (119), genetic predisposition (107), or HLA phenotype (19).

In the routine management of diabetics, I think that a few simple measures should be done annually to screen for neuropathy.

First, specific questions should be asked regarding numbness, tingling, and pain. If pain is present, then the location and nature should be described. Diabetic pain commonly is most severe at night, or when the patient is at rest. Questions about autonomic function should be included (impotence, postural hypotension, visual blurring, abdominal bloating and cramps, diarrhoea, hypoglycemic unawareness, sweating abnormalities). Following the history, a brief examination should be done. The patient's musculature should be examined for any wasting, or weakness. The deep tendon reflexes should be assessed. The primary sensory modalities (light touch, pinprick, temperature, position and vibration) should be checked. Additionally, supine and standing heart rate and blood pressures should be measured; and the pupils examined. The above should be included as part of the routine annual assessment of diabetic patients done by the primary physician and/or diabetologist.

If this screen is positive, then the patient should be reviewed neurologically, including electrophysiological testing, to fully document the neuropathy. Such documentation would include conduction studies of the sural, peroneal motor, and median motor and sensory nerves.

Autonomic Neuropathy

Clinical autonomic neuropathy, excluding impotence, occurs infrequently in the diabetic. However, in those symptomatic patients, autonomic involvement is often associated with peripheral sensorimotor neuropathy (134,77,152). Most often, autonomic neuropathy is asymptomatic (78,103). However, those few patients having symptomatic autonomic neuropathy (excluding impotence) do have an increased incidence of sudden death probably due to cardiac arrhythmias and sudden death (53). However, the commonest clinical problem is that of impotence in the male diabetic population. This symptom is frequent, occurring in approximately 50% of male diabetics (50). If detailed electrophysiological studies are performed on diabetics including penile erectile function, blood pressure and evoked response testing, then approximately 90% of male patients with insulin dependent diabetes mellitus have abnormalities, suggesting that diabetic impotence is almost always neuropathic in origin (Bradley, Colorado, 1984). In these instances, psychological counselling may be beneficial, and consideration should be given to surgical implants. As with the peripheral neuropathy, autonomic abnormalities can be detected by specialized investigations in asymptomatic patients. For example, bladder dysfunction occurs in about 60% of insulin dependent diabetics if testing includes cystometry, sphincter EMG, uroflometry, urethral pressure profiles and EEG's (21). Cardiovascular function tests are available, although not widely employed; these include the variation in the R-R interval and other tests for sinus arrhythmia (20,77,108,147). These studies indicate decreased parasympathetic tone and become abnormal within two years of a diagnosis of diabetes mellitus (108).

Symptomatic autonomic neuropathy can mimic different visceral disorders and should be considered in the management of diabetics. This entire area requires more research (20).

Peripheral Vascular Disease

The association between significant peripheral vascular disease and peripheral neuropathy in the diabetic is unclear. There is a poor correlation pathologically between the degree of small vessel disease and neuropathy (34,42,47,134,135). In non-diabetic patients with severe occlusive peripheral vascular disease resulting in amputation, the degree of neuropathy is not comparable to that seen routinely in diabetic nerve even in those diabetics without clinical neuropathy (134,135). Therefore, the role of peripheral vascular disease in diabetic peripheral neuropathy is unclear.

Electrophysiological Studies

Conventional nerve conduction studies and electromyography are used to document diabetic neuropathy objectively. An abnormal study suggests that the patient has diabetic neuropathy. Studies on diabetic patients have shown that 75% of newly diagnosed diabetics without clinical neuropathy have some abnormality of nerve conduction (152). However, patients with symptomatic diabetic neuropathy have a greater degree of abnormality on electrophysiological testing than diabetic patients without neuropathy (76,54). An abnormal nerve conduction study does not clearly indicate that the patient has, or will have clinical neuropathy. However, this parameter is used in patients with neuropathy as an objective measure of the neuropathy, and to assess responses to therapy (3,9,17,26,16,40,44,70,71,55). The only other parameters available include subjective clinical symptoms and objective clinical findings. The reproducibility of conventional nerve conduction studies is in some doubt (61,81). There is uncertainty as to whether all the decrease in conduction velocity observed is reversible, or irreversible; although the latter is more likely (9,64). In addition, nerve conduction studies measure the function of large fibre function only, and not the activity of the small fibres. Therefore, the nerve fibre population studied is limited.

Although conventional nerve conduction studies and EMG are useful in documenting the extent and severity of neuropathy in diabetics with clinical evidence of neuropathy, some of the above considerations have led to the development of newer quantitative methods in an effort to increase the sensitivity of detection, and extend the scope of the investigations. These include measurement of somatosensory evoked potentials (101), quantitative motor unit estimates (76), nerve fibre conduction velocity distributions (39,43) visual evoked potential testing (110), plantar nerve sensory studies (112), and proximal conduction studies (59). Other newer electrophysiological techniques are under review. Single-fibre EMG in the tibialis anterior muscle of diabetic patients has been tested in this laboratory. All patients with diabetic peripheral neuropathy studied have increased jitter and fibre density (VB, 1984). Daube (Keystone, 1984) reviewed 27 diabetics without neuropathy, and found 2 with elevated jitter and 5 with increased fibre density.

Metabolic Control and Peripheral Neuropathy

The exact relationship between chronic hyperglycemia and development of neuropathy is unclear. The neuropathy is more prevalent in those diabetics who have had poor control and who have been diabetic for longer intervals (107). Results from studies using conduction tests as the measure of diabetic neuropathy are contradictory. Greene (64) has suggested that nerve conductions will not change in six months, even though diabetic control, as measured by glycosylated hemoglobin is improved. Early studies evaluated diabetic control by monitoring blood glucose levels (9,70,71), a less precise way than measuring the glycosylated hemoglobin level. For example, in a study by Lamontagne and Buchthal (90), thirty diabetic patients with neuropathy had abnormalities in conduction studies which developed concomitantly with, and were an integral part of, the metabolic disturbance. However, the only electrical measure that correlated with the severity of the neuropathy was the decrease in peroneal nerve conduction velocity, and none of the conduction studies correlated with the duration, or severity of diabetes. Sensory potential changes are the most sensitive electrophysiological indicator of peripheral neuropathy (90,44). A variety of studies have not shown any improvement in sensory conduction with improved diabetic control (3,61,62,64,90,105,109,117). Noel (101) showed abnormal sensory function in 11 of 26 diabetic patients without neuropathy. Mulder indicated that 43 of 103 unselected diabetic patients had abnormal clinical and electrophysiological testing (98). Behse and Buchthal (9) showed 12 of 12 patients with diabetic neuropathy had abnormalities on electrophysiological testing which persisted for intervals of up to 8 years. Insulin therapy appears to improve conduction velocity in motor nerves of newly diagnosed diabetics (141). Improved glycemic control in non-insulin dependent diabetics results in faster median nerve motor conduction velocities (109). A correlation between decreased peroneal nerve motor conduction velocity and poor glycemic control has also been demonstrated (61). Both median and peroneal motor conduction velocities improve in correlation with glycemic control (61,109). Reports on changes in conduction and neuropathy following therapy with the portable infusion pump are contradictory with some investigators documenting improvement (105,27,57) and others showing no effect (117). Interestingly, a failure of the peroneal motor conduction velocity to correlate with the duration of diabetes or degree of metabolic control has also been recorded (55,90). In general, however, it appears that the presence and severity of peripheral neuropathy as shown by nerve conduction and EMG studies do correlate with the duration and severity of diabetes mellitus. Furthermore, the nerve conduction abnormalities are more severe in those who have poorly controlled diabetes. Motor conduction improves with improved glycemia control, although sensory studies do not. Therefore, electrophysiological monitoring is useful, although rapid changes should not be expected. In addition, permanent abnormalities are present, and full recovery should not be expected. Reasons for the variability in these reports might include heterogeneity of the patient population, differing severity of neuropathy, differing treatment intervals, and differing levels of diabetic control achieved in the studies. Since conventional studies measure only the large fibre population, other newer methods of neurophysiological investigation are necessary. Double stimulation motor studies, proximal nerve conduction studies and single-fibre EMG studies are some examples of these newer techniques. Computerized assessments of EMG might also extend our investigative abilities.

It is important to have a means of measuring small fibre involvement. Sensory threshold determination of, for example, thermal, or painful stimuli might be useful. Autonomic tests also indicate small fibre involvement (108).

Therapy

How can we treat diabetic neuropathy? First, we must diagnose the disorder by means suggested earlier in this paper. The next step is rigorous control of hyperglycemia. This involves educating the patient about the complication, and about the role of strict control. New therapeutic modalities which are being tested in research centres include insulin infusion pump therapy (14,57,113,117), aldose reductase inhibitors (75,84,86,93,153), and gangliosides (1,7,37,41,54,74,82, 100). Pancreatic islet cell transplantation in animals holds future interest for humans (116). Once the diagnosis is established, the primary diabetologist or physician looking after the patient should follow the patient every 2-3 months and rigorously review the diabetic control. A neurologist with EMG expertise should follow the patient annually. Detailed autonomic testing is needed in those patients with autonomic symptoms, or abnormalities on examination.

Improved diabetic control is the only specific therapy for diabetic neuropathy which is generally available. Symptomatic control of the patient's pain may be achieved by analgesic medications, anticonvulsants (diphenylhydantoin, or carbamazepine), or amitriptyline. The addition of fluphenazine is not advised by certain authors (24). Entrapment neuropathies are frequent in diabetic patients who show increased sensitivity to pressure palsies (98). Therapy directed to the specific entrapment may be beneficial (24). Treatment for various autonomic problems includes: psychological counselling, and surgical implantation for impotence; regular voiding, and prophylactic antibiotics for bladder atony; elastic stockings, and fludrocortisone for orthostatic hypotension; and metoclopramide for gastroparesis and diabetic diarrhea.

In summary, diabetic neuropathy is a frequent and difficult problem. The disorder is heterogeneous both in clinical expression and pathophysiology. The prolonged metabolic abnormality (i.e. hyperglycemia) appears to be a major factor in the development of peripheral nerve dysfunction, and this might be complicated by ischemia due to vascular lesions.

Excitement regarding the therapy of diabetic neuropathy has been generated by the potential use of aldose reductase inhibitors. Their use is based on observed metabolic derangements in diabetic nerve including: increased polyol pathway activity, decreased myo-inositol content, and decreased Na-K-ATPase activity. In the animal model, therapy with an aldose reductase inhibitor can prevent or reverse these changes (63,64,65,66,67,68,69). In addition, diabetic patients show some improvement in their conduction velocities following therapy with sorbinil, an aldose reductase inhibitor (86). The exact mechanism by which aldose reductase inhibitors work is unclear. Studies are underway to determine whether these agents improve the clinical and electrophysiological abnormalities in human diabetic neuropathy.

Recommendations

1. Clinical

Diagnosis of diabetic neuropathy is essential for proper therapy. This may be achieved by:

(a) primary physician education concerning an annual review for neuropathy, including appropriate referral for documentation, as detailed in the body of the report, and the necessity of strict control in the patient population, and

(b) patient education concerning the existence of diabetic neuropathy with a simple outline of symptoms and signs presented in a pamphlet which could be made available in physicians' offices. The therapeutic necessity for strict control should be included.

2. Research

Research in many areas of diabetic neuropathy is necessary, and should be supported.

Clinically, we must develop quantitative methods of assessment (eg: computerized electrophysiological tests, quantitative sensory threshold determinations, autonomic function tests) to give objective measures which might be followed to better assess responses to therapy.

Further research into the pathophysiology (metabolic disturbances, ischemia) is necessary to allow the development of rational modes of therapy. This should be done in human subjects as well as in animal models.

Different modes of therapy must be tested rigorously. These include modalities such as: prevention of complications by strict diabetic control, metabolic intervention (eg: aldose reductase inhibitors), and pancreatic islet cell transplantation.

The future looks encouraging.

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DIABETES AND MACROVASCULAR DISEASE
MAGNITUDE OF THE PROBLEM
George Steiner, M.D.

Atherosclerosis is the most common complication of diabetes in the Western world. In 1938, Warren recognized that atherosclerosis occurs both at a younger age and in a more severe form in those with diabetes than in those without diabetes. Before insulin therapy became available in 1922, atherosclerosis was responsible for only 16 to 23% of the deaths occurring in Joslin Clinic patients. However, since the advent of insulin therapy, diabetics have survived longer and the mortality patterns have changed. Today 75 to 80% of those with diabetes die of the consequences of arteriosclerotic disease. This contrasts with nondiabetic North Americans, one-third of whom die of atherosclerosis-related disorders.

The data from a large prospective study undertaken in Framingham, Massachusetts underline the magnitude of the problem with respect to both morbidity and mortality. In diabetics, the morbidity due to coronary heart disease is doubled. Morbidity caused by cerebrovascular disease is more than doubled, and that due to intermittent claudication is more than quadrupled. Furthermore, with all problems except for peripheral vascular disease, the increase among diabetic women is at least as great as that among diabetic men. Outcomes are similar with respect to mortality. Again, the increase in cardiovascular mortality among insulin-taking diabetic women is five times that seen among insulin-taking men. The mortality among those with diabetes not on insulin therapy is equal in both sexes. This sex incidence contrasts with the relative immunity to arteriosclerosis enjoyed by nondiabetic women.

Recently, there has been a small but significant decline in the mortality due to heart attacks in Canada. However, there is no knowledge to indicate whether this is in diabetics as well as in non-diabetics.

Scope of the Report

Atherosclerosis is the most common complication found in diabetics today. One can approach this complication from two perspectives: prevention and therapy. The latter involves the treatment of the ischemic injury to the heart, central nervous system or extremities. In that regard, treatment is no different, for the most part, in the diabetic from that in the non-diabetic. Some differences between the diabetic and the non-diabetic include the possibility that ischemic neurologic damage is greater in the individual whose plasma glucose is elevated. The Framingham data suggest that congestive heart failure can exist independent of ischemic heart disease. The coexistence of microvascular and macrovascular disease may add problems to the management of ischemia. Finally, the management of an acute illness in the presence of the metabolic derangements of diabetes is more complex than it is in the non-diabetic. However, the survival immediately after a myocardial infarct in diabetics is similar to that in non-diabetics. In fact, for the most part, the management of ischemic end organ damage in diabetics is very similar to that in non-diabetics and so will not receive further consideration here. Rather, this report will focus on prevention. This, although less dramatic, will be of more benefit to the diabetic and his society in the long run. To take this approach, we will have to look for underlying causative factors. The key conclusion will be that our knowledge is dismally lacking and so our first task will be to study the problem in general and in diabetics in particular. Many studies, at least of the pathology of atherosclerosis, suggest that the process in the diabetic is similar to that in the non-diabetic. Hence, some of our present information will be drawn from the field of atherosclerosis in general. However, one of our tasks will be to ask, at each step of our path to knowledge, "Is this also applicable to diabetes"?

EPIDEMIOLOGY

Background

A number of risk factors for cardiovascular disease have been identified in epidemiologic studies in both the general and diabetic populations. They include hyperlipidemia, hypertension, smoking. There is less certainty about obesity. Although it is accompanied by a high risk of coronary disease, this may be due to the association of obesity with other risk factors (hyperlipidemia, hypertension) rather than to the obesity itself.

Hypertriglyceridemia is the most common form of hyperlipidemia found in those with diabetes. Many have felt that it is one of the factors responsible for the accelerated atherosclerosis seen in diabetes. However, there is considerable controversy about the influence of hypertriglyceridemia on atherosclerosis, at least among non-diabetics. The Framingham study data suggest that although elevated concentrations of very low-density lipoproteins (VLDL) are associated with increased coronary artery disease risk, this is due to the accompanying hypercholesterolemia. The results of a recent prospective study of Stockholm men dispute this, suggesting that hypertriglyceridemia is an independent risk factor. Some resolution to this controversy may come from the suggestion that hypertriglyceridemia poses a risk in those who have familial combined hyperlipidemia, but not in those who have familial hypertriglyceridemia.

Recently, it has been shown that high-density lipoprotein (HDL) may also influence the risk of coronary artery disease. However, the influence of HDL differs from that of other lipoproteins, for increases in HDL diminish the risk of ischemic heart disease (IHD). One example of the protective effect of HDL is shown by the data obtained in a study of the 176-member Newfoundland kindred. Those members of the kindred in the quartile with the highest HDL levels had no IHD. This study also showed that IHD was not found in individuals whose ratio of HDL-cholesterol (HDLC) to LDL-cholestrol (LDLC) exceeded 0.2.

Epidemiologic studies have found virtually every possible combination of changes in HDL levels in those with diabetes. Some found that diabetes have reduced levels of HDL. Others found this reduction only in female diabetics. Still others found no change in the HDL levels of diabetics. Good diabetes control, in some studies, but not in others, was found to be associated with reduced HDL levels. Finally, HDL levels may actually be increased in some diabetics, particularly those who are treated with insulin.

The increased risk of atherosclerosis in those with diabetes could be a consequence of an increase in the frequency of some or all of the foregoing risk factors. On the other hand, it may be independent of them and could be either a direct consequence of diabetes itself or of other intermediate factors. The Framingham data suggest that both may apply, for only 20 to 30% of the increase in arteriosclerosis associated with diabetes is due to an association with one of the risk factors noted above. Another factor related to a high incidence of coronary atherosclerosis in those with diabetes is hyperglycemia. The high incidence of IHD in relation to hyperglycemia persisted in these studies even after adjusting for other known risk factors. However, there may be a number of unknown risk factors that could accompany hyperglycemia and that may influence the prevalence of cardiovascular disease. For instance, the association with hyperglycemia could be due to microangiopathy, or use of oral hypoglycemic agents (sulfonylureas, phenformin) or insulin with failure to produce satisfactory metabolic control, or to differences in the type of diabetes (IDDM or NIDDM) and differences in the influence of risk factors for atherosclerosis in the two types. Another factor that may be linked to atherosclerosis is hyperinsulinemia. This can be found both in the diabetic who is treated with insulin and in the non-insulin-dependent diabetic. It should be apparent that virtually no single mechanism will be found to link all aspects of two disorders as multifaceted as diabetes and atherosclerosis. The uncertainty about much of the available epidemiologic data highlights the need for more carefully collected and analyzed epidemologic, pathologic, and biochemical data.

We in Canada have a unique opportunity to study the impact of race and environment on atherosclerosis. A number of studies have shown that although atherosclerosis is less common in Japanese in general, it is still more common in Japanese diabetics than non-diabetics. We could compare the epidemiology of diabetes among our first and second generation immigrants with and without diabetes to that existing in their countries of origin. Another opportunity lies in our native population. It is known that the Hopi, Navajo and Pima with diabetes are less prone to macrovascular disease than are Caucasians. Does the same exist in our Indian and Inuit populations?

Recommendations

1. Examine changing morbidity and mortality patterns in macrovascular disease with particular attention to the patterns in diabetics.
2. Seek further epidemiologic information about newly suggested risk factors in diabetics.
3. Characterize the patterns of atherosclerotic disease among the diabetics of different racial populations in Canada in an attempt to learn about the possible causative factors from the differences.
4. In all of the above, relate data to the nature of the diabetic. (NIDDM vs IDDM; Treatment method; Obesity; Sex etc).

CLINICIAL DETECTION OF MACROVASCULAR DISEASE

Background

In the past several years, much attention has been devoted to the development of non-invasive methods to assess coronary, peripheral, and extracranial arteries. Any studies of disease prevalence or of effectiveness of preventive or treatment measures will require sensitive and specific methods to assess the arterial tree non-invasively. The present methods include exercise testing, radionuclide imaging, Doppler velocimetry, and ultrasonic imaging.

Recommendations

1. Validate existing and, where necessary, develop new methods.
2. Apply above to epidemiologic studies.

LIPOPROTEINS, ATHEROSCLEROSIS, AND DIABETES

Background

The heterogeneity of lipoproteins is increasingly apparent. In order to understand the metabolism of lipoproteins, their role in atherogenesis, and their epidemiologic role as risk factors, it is no longer sufficient to speak of chylomicrons, VLDL, LDL, and HDL. We must seek a better understanding of the subclasses of lipoproteins. For example, the remnants of triglyceride-rich lipoproteins (also called IDL or beta VLDL) are probably an atherogenic fraction that may be important to examine when considering the atherosclerotic potential of hypertriglyceridemia. Similarly, the atherogenic impacts of HDL_c and of "light" vs. "heavy" LDL, to name just two, must be explored.

Recommendations

1. Establish definitions of the subclasses of lipoproteins, based on their function.
2. Develop methods to separate these subclasses. If epidemiologic studies are to be done, these methods must be simple enough to apply to large numbers of samples.

3. Study the factors regulating the metabolism of these subclasses, and study their epidemiologic links to atherosclerosis. These studies must be conducted not just in non-diabetics, but also in diabetics.

Background

The complexities of the nature of various apolipoproteins has become more apparent. This has included the identification of two forms of apoB; the knowledge of the amino acid abnormalities in the isoforms of apoE; the identification of diseases resulting from genetic deficiencies of apolipoproteins, such as abetalipoproteinemia and apoCII deficiency. In addition, it has become apparent that in diabetics there is a non-enzymatic glycosylation of apoB and there may be a change in the relative proportions of apoCII/apoCIII.

These apolipoprotein alterations may influence the metabolism of lipoproteins, their interaction with cell-surface receptors, their ability to activate lipoprotein lipase. In addition, the quality of apoB may reflect the number of particles in the VLDL-LDL family, and that of apoAI in the number in HDL.

Recommendations

1. The nature of the apoproteins in the lipoproteins must be further defined in both normals and diabetics. This includes an exploration of the two forms of apoB, the isoforms of apoE, the proportion of apoCII/apoCIII, and the glycosylation of apoB in diabetics.
2. This knowledge should then be applied to the quantification of lipoproteins in the plasma of diabetics and to the study of lipoprotein metabolism in diabetics.

Background

Methods are, or soon will be, available to characterize the kinetics of the different lipoprotein components; to study lipoprotein receptors on different cell types; to examine the lipolytic enzymes involved in lipoproteins in catabolism. It is apparent that in the diabetic (both IDDM and NIDDM) hyperinsulinemia may be very important in regulating lipoprotein metabolism.

Recommendations

1. The newly available methods should be applied to the study of lipoprotein physiology in normal and diabetic states (again differentiating between the types of diabetes).
2. The impact of glycemia control methods, including various systems of insulin delivery, must be evaluated with respect to their role on lipoprotein physiology.

Background

Most epidemiologic studies relating to dyslipoproteinemias and atherosclerosis (for example, the Lipid Research Clinic Coronary Primary Prevention Trial) have either excluded diabetics or not characterized their diabetes sufficiently. By contrast, most studies of diabetics have paid little attention to a detailed examination of their vascular status in relation to their lipoprotein status or have been limited by the small numbers of patients studied. Further, most studies have tended to lump diabetics into one group.

Recommendations

1. Detailed epidemiologic studies of the prevalence and genetics of diabetes are still needed.
2. The relation of lipoprotein and other risk factors in diabetes to vascular disease in the coronary, peripheral, and cerebral vascular beds must be conducted.
3. Ultimately, it will be necessary to test the effect of treatment to reverse risk factors (via glycemic control or other means directed at the risk factors themselves) on the development of vascular disease.
4. The effect of various regimens to treat diabetes (diet, exercise, hypoglycemia agents) on risk factors must each be evaluated.
5. All epidemiologic studies must consider the different types of diabetes separately.

HYPERINSULINEMIA AND ATHEROSCLEROSIS

Background

There are a number of epidemiologic studies that suggest that hyperinsulinemia may be an independent risk factor for atherosclerosis. There have even been studies suggesting that hypertensives respond to glucose challenges with abnormally high insulin responses. Unfortunately, each study still has some limitations, either by virtue of limited numbers studied or by virtue of having restricted the studies to males. Furthermore, they did not examine diabetics.

The suggestions of an epidemiologic association of hyperinsulinemia with atherosclerosis receive support from pathophysiologic studies. They show that insulin stimulates the growth of certain cells (adipocytes, fibroblasts and arterial smooth muscle cells). Its effect on the growth of others is less clear. The growth of endothelial cells from retinal capillaries is stimulated much more than is that of aortic endothelium. This also raises the importance of differentiating between types of endothelial cells. Insulin can also slow the regression of experimentally induced atheromata. An associated observation is that hyperglycemia can decrease endothelial cell replication, raising the possibility that hyperglycemia may inhibit endothelial call repair after injury. Parenthetically, it has been observed that insulin increased aortic glucose uptake in vitro but only if the aortae are under normal perfusion pressures.

Recommendations

1. Examine, with appropriate epidemiologic design, the atherosclerosis risk effect of hyperinsulinemia in both non-diabetics and non-insulin dependent diabetics of each sex. Examine whether any associations are specific for one or other vascular bed.
2. In insulin-treated diabetics (pump or multiple-injection) examine whether hyperinsulinemia can be linked to the development of atherosclerosis. This obviously will require easy and accurate assays for free-insulin in this population.
3. Define the appropriate endothelial cell to serve as a model for human macrovascular endothelium.
4. Develop methods to study aortae in vitro under normal arterial pressure over sufficient time intervals to examine potentially atherogenic processes.
5. Develop methods to grow arterial cells from human sources.

PLATELETS & PROSTAGLANDINS IN DIABETES

Background

The importance of the materials released from platelets in atherogenesis is very relevant. These include a variety of vasoactive, thrombogenic and growth promoting factors. The role of diabetes in altering platelet function is still a matter of considerable controversy. The pathophysiologic role in atherosclerosis of these factors is not yet fully elucidated. The therapeutic and preventive potential of cyclooxygenase inhibitors is still under tests. Canada has a number of centres that can and are contributing knowledge in these areas.

Recommendations

1. Further research into the role of cellular elements in atherogenesis.
2. Evaluate the potential for drugs that modify platelet function to play a preventive role in diabetics.

HYPERTENSION

Background

There is considerable disagreement about the effect of diabetes on blood pressure. Keen and colleagues feel that if the populations are closely matched, blood pressure among diabetics does not differ from that among non-diabetics. This contrasts with the data from Framingham, Massachusetts and that from Tecumseh, Michigan. In the former community, the blood pressure of diabetics, especially diabetic females, was greater than that of non-diabetics. In the latter community, females but not males with diabetes had a higher blood pressure than did non-diabetics of the same sex. The strongest data linking hypertension in diabetics to IHD are from a study of employees ofthe DuPont Company. The prevalence of hypertension was 54% greater among the diabetics in this population than it was among the non-diabetics. Furthermore, IHD among the diabetics with hypertension was twice as common as it was among either the normotensive diabetics or among the control subjects. Clearly hypertension in the diabetic plays other significant roles as well, accelerating renal damage, predisposing to toxemia, etc. However, those lie outside the scope of this review.

Recommendations

1. Establish the epidemiologic relationship between diabetes and hypertension, if any, and define the particular population at risk.

SMOKING

Background

There is much dispute about the frequency of smoking among diabetics. Some claim it to be higher, others lower than in the general population. Whatever the case, the link between smoking and macrovascular disease is clear. Hence, for any individual patient, advice against smoking should be given. Unfortunately, the success rate in stopping smoking is very low.

Recommendations

1. Develop new anti-smoking strategies.

PERIPHERAL ARTERIAL DISEASE

Background

Although the previous portions of this manuscript deal with prevention of atherosclerosis, this portion will deal with prevention of end-organ ischemic damage. The difference between diabetics and non-diabetics with respect to macrovascular disease is greatest in the peripheral arteries. Morbidity is four times greater among diabetics than among non-diabetics. This is most pronounced in diabetics who smoke. Diabetes is the leading underlying cause of lower extremity amputations. Much of this can be avoided even in the presence of arterial insufficiency by avoiding injury to the extremity with the resultant increase in blood flow requirements.

Recommendations

1. Improved education of patients and medical personnel with respect to prevention; and management of food problems.
2. Development of better non-invasive assessment tools.
3. Strict avoidance of other risk factors, particularly smoking.

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TREATMENT

TREATMENT OF DIABETES
SUMMARY AND RECOMMENDATIONS

Each of the discussants on this committee reviewed the assigned topic and proposed a number of conclusions and recommendations which were reviewed, modified where necessary, and agreed by the committee. The full list of these conclusions and recommendations appear in the text. In many cases it is apparent that there are important specific areas in which information must be gathered, and these are indicated. For each topic also, a number of specific research questions were proposed. It is recognized by the committee that each of these recommendations and also those brought forward in this summary carry major implications in terms of cost, which have to be addressed in relation to the total funds necessary, and the sources and mechanisms appropriate for provision of these funds. These problems must be dealt with by the Task Force, if these recommendations are to be put into effect.

The conclusions and recommendations summarized below will be presented in relation to each of the topics addressed. In addition the committee agreed a smaller number of major recommendations to which it would accord a high priority, which are also set out under the heading of general recommendations.

Trends in the Therapy of Diabetes Mellitus

These conclusions and recommendations are divided into those related to the demands of current optimal standard therapy, and those related to ongoing and future development of improved and innovative methods of therapy.

A. Current Therapy of Diabetes of Diabetes Mellitus

It was agreed that the minimum requirements in this area are the establishment of guidelines for therapy and assurance that the facilities and services necessary for such therapy are in place. Therefore, the recommendations are:

(1) to establish an agreed set of guidelines for health care delivery to diabetes mellitus. It is suggested that this should be addressed by an appropriate working group identified by the Task Force in collaboration with the Canadian Diabetes Association and the Quebec Diabetes Association

(2) To undertake an assessment of the facilities and services at presently available for the treatment of diabetes across the country, in order

(3) to identify shortcomings and to satisfy the needs as determined in this way.

B. Development of Improved and Innovative Therapies in Diabetes

It is concluded that it is necessary to determine the optimum special system for such developmental needs. The recommendations are:

1. Appropriate model systems for development and assessment of the efficacy of improved therapy in diabetes should be established. A number of possible models were discussed. These range from institutional diabetes research centres, through collaborative organizations with appropriate administrative support and funding. It is suggested that a committee of the Task Force address this problem. The workshop discussed the nature of funding for such research. It was agreed in general that the peer review mechanism is the best established method for determining the merit and priority of proposals in this area. However, it is also suggested that the funding mechanism for this type of work needs to be separated from the established competitions for more basic research related to diabetes. Work in the area of development of improved therapies might be regarded as a category of research and development within the health care system so that existing and possibly new funding arrangements developed through the provincial and federal ministries of health might be explored.

2. As a second recommendation in this area the workshop recognized the importance of training a suitable cadre of health professionals. These professionals would include physicians developing special expertise in optimal and innovative therapies in diabetes and might be trained within the model systems discussed above. They would compete for personal support through a process separate from that currently established for research trainees seeking experience designed to qualify them as independent investigators.

C. Diet in the Management of Diabetes Mellitus

Summary

1. At the present time a systematic and standardized training program for dietitians specializing in diabetes mellitus does not exist.

2. In Canada there is a national shortage of dietitians with special training in diabetes. This shortage is exacerbated by the maldistribution of the existing dietitians.

3. Many physicians lack the time and/or the specialized knowledge and skills required for effective diet counselling in diabetes.

4. The present system of funding and reimbursement for the services of dietitians serves to limit the access of diabetic patients to appropriate professional advice.

Recommendations

1. It is recommended that the curricula for medical and dietitic students be improved to provide adequate training in the dietary management of diabetes.

2. It is also recommended that certification programs for health care professionals specializing in dietary management of diabetes be established. The programs should include requirements for internships, and might be related to systems for continuing education.

3. In order that there be an adequate supply of dietitians, there should be (a) adequate provincial government funding of dietetic internships in teaching hospitals and (b) hospital budgets that encourage preventive care, e.g. outpatient counselling, diabetes education.

   To secure accessibility to diet counselling in the community outside hospitals, the fees of qualified dietitians should be covered directly or indirectly by provincial health care plans.

D. The Use of Oral Hypoglycemic Agents in Treatment of Diabetes Mellitus

Summary

It is concluded that there are important inconsistencies in the use of the oral agents in therapy in diabetes. These usages sometimes do not take account of agreed indications and contraindications for prescription of the various agents.

Recommendations

It is recommended that up-to-date information regarding therapy with oral hypoglycemia agents be included in the proposed guidelines for the management of diabetes mellitus.

E. The Use of Available Preparations of Insulin in the Treatment of Diabetes Mellitus

Summary

It is concluded that confusion and uncertainty exist regarding the properties, and indications for the selection of the variety of preparations of insulin now available.

Recommendations

1. The development of an appropriate generic terminology is recommended. This should be undertaken with good liaison between health professionals, manufacturers, and the appropriate regulatory agencies.
2. Further liaison should be developed between the health professionals and the manufacturers in order to provide for continued assessment of the availability and need for particular preparations.
3. The workshop concluded also that there remain good reasons for support in principle of the maintenance of an onshore capacity for production of a full range of insulins.

F. Management of Diabetes in Pregnancy

Summary

1. It was concluded that although guidelines and standards for the management of diabetes in pregnancy are well established in general, the details of current practice and the outcomes of pregnancies in Canada are unknown in many areas of the country.
2. The complement and education of health care providers in this area of diabetes management are inadequate, to an uncertain degree.
3. A suitable screening mechanism for diagnosis of gestational diabetes mellitus has not been defined.

Recommendations

1. A standardized screening test for gestational diabetes mellitus must be established.
2. It is recommended that consumable materials and apparatus necessary for optimal therapy of diabetes in pregnancy should be provided without charge to this group of persons with diabetes.
3. It is recommended that a registry for diabetes in pregnancy should be established. The objective of this registry in the context of the therapy of diabetes is to provide a means for quality control.
4. The assessment of outcome in a systematic way must be undertaken, for the above reasons.
5. It is important to emphasize that preconception management of diabetes must be appropriate and generalized.

G. Management of Diabetes in Children

The workshop recognized the importance considering the treatment of diabetes in children as a special problem.

Summary

1. It was concluded that provision of appropriate education and health care to diabetic children is commonly inadequate.

2. It is also concluded that up-to-date information related to childhood diabetes and its management is not systematically reaching the primary care physician or the child with diabetes and his/her family.

Recommendations

1. It is important to obtain information regarding the current level of delivery of health care to children with diabetes across the country.

2. It is recommended that specific guidelines and standards for the management of diabetes in children be established and disseminated.

3. It is also recommended that specific goals for professional education in regard to management of diabetes in children be set.

4. It is imperative to establish the funding-reimbursement mechanisms do not impede delivery of the necessary services.

H. General Recommendations

The following recommendations were adopted by the workshop and accorded high importance and priority.

1. It is necessary to prepare an up-to-date set of guidelines for the professional management of diabetes, as indicated above.

2. It is urgently necessary to undertake a review of the available manpower and facilities in relation to the needs as related to the standards defined, and to determine the shortfall in funding and the sources of monies necessary for solutions to this problem.

3. It is important to determine and establish a system or systems for the development and assessment of improved and innovative modes of treatment in diabetes mellitus.

4. There are compelling reasons for provision of consumable materials and apparatus to identifiable groups of persons with diabetes, including children, pregnant women and the elderly. It is also important to consider the necessity, and means of extending this assistance to persons with diabetes in general.

5. There is a need to establish registries for diabetes. Initially these should be set up for diabetes in pregnancy, and for persons with newly diagnosed type 1 diabetes. The objective in the treatment context of these registries would be (a) to provide for assessment of outcomes, quality control, and appropriate corrective responses, and (b) to assist in identification of families and persons at relatively high risk for development of diabetes. This information is also necessary for assessment of risk-benefit ratios in this important area of health care.

CURRENT TRENDS IN THE THERAPY OF DIABETES MELLITUS

John Dupré, F.R.C.P.

Introduction

When insulin became available for the treatment of diabetes the accepted clinical picture of the disease represented what is now recognized as the insulin-dependent variety. Insulin therapy was developed empirically, but in accordance with earlier experience of replacement treatment for an endocrine-deficiency state. Such treatment of hypothyroidism for example had provided a model which was not invalidated by the inconvenient fact that the new hormone had to be administered parentrally. However, the experience gave no hint of the lability of requirements that later proved to be a feature of insulin therapy. The recognizable clinical and metabolic disorders in diabetes provided endpoints for assessment of control of the disease. For over two decades the criteria for good control could be reduced to the elimination of symptoms, with prevention of ketonuria and extremes of glycosuria. With the development of long-acting insulin preparations this could be achieved with relatively simple treatment regimens and resulted in apparently normal growth and development in children and adolescents. Conceptually, this approach is similar to that employed at present. However, recognition of multiple endocrine and metabolic abnormalities has increased the stringency and complexity of criteria for control. It remains apparent that it is rarely possible to "normalize" the multiple pathophysiologic features of diabetes by means of presently available therapies.

The various clinical characteristics of diabetes emerged through experience of its management under these conditions, with definition of apparently insulin-sensitive and insulin-resistant varieties that correspond roughly to what are now classed as insulin-dependent (IDDM) and non-insulin-dependent diabetes (NIDDM), and the description of the so-called complications of the disease developed. The vascular and neurological complications are now the dominant problem in management of diabetes. At the clinical level, recent trends in therapy of the disease are dependent on the working assumption that the complications are at least in part causally related to recognizable disorders of intermediary metabolism and its control mechanisms, in both insulin-dependent and non-insulin-dependent. At the investigational level, the relationship between endocrine-metabolic abnormalities in diabetes and the morbidity of the condition is under intense scrutiny. In insulin-dependent diabetes mellitus, new hypotheses for the etiopathology have led to clinical trials of experimental therapies. These offer exciting possibilities for preventive applications that may be capable of ameliorating the metabolic disorders and the complications of diabetes. As a result, attention is directed to increasingly refined descriptions of the prodromal and early phases of NIDDM as well as IDDM, as stages of the disease in which established and new therapies must be tested.

CURRENT TRENDS IN THE THERAPY OF DIABETES MELLITUS IN CANADA

Metabolic Control: Objectives and Techniques

Current strategies in the management of diabetes by means of conventional therapies have been strongly influenced by recognition of the correlation between metabolic control and the development of complications of the disease (1,2,3). The inference that glycemic control can affect the morbidity of diabetes was supported by the results of animal experimentation (4,5). This situation led to development in the late 1970's of a consensus that optimized control of glycemia should be the general objective, this goal being tempered by the need to avoid unacceptable risks or inconvenience to persons with diabetes (6). Under this umbrella, diverse views about the feasibility and safety of efforts to maintain near normal glycemia are still debated (7,8). This problem is central to issues regarding techniques and systems for delivery of health care in diabetes mellitus. Until the question is settled, it is not likely that the approach to management will be substantially and systematically changed. This is not the place to discuss the details of the scientific controversy. However, it is important to note that the outcomes of current experimental approaches to this question may provide important new information and should have major impacts on the treatment of diabetes at large within the next few years.

Replacement Treatment With Insulin in Diabetes

An important component of investigation of diabetes since the discovery of insulin has consisted in studies related to the physiology of replacement treatment of insulin-deficient states. Investigators in this country have made substantial contributions to this work. After the initial experience with administration of insulin in IDDM, descriptions of the effects of insulin deficiency on intermediary metabolism and its regulatory mechanisms were expanded at rates largely dependent on technological developments. By the 1960's it became possible to contemplate the elaboration of the so-called artificial endocrine pancreas, a system for delivery of insulin, with or without glucagon, according to the concentrations of glucose in the blood. Outstanding contributions were made in this field by Canadian investigators (9,10). On the background of experimental evidence thus obtained in insulin deficient animals, and in human volunteers with type 1 diabetes mellitus, a number of research groups tested the feasibility of treatment with insulin making use of portable infusion pumps or multiple injection regimens under everyday conditions, omitting continuous monitoring of levels of glucose in the blood, but relying on "self blood glucose monitoring" by the patient (11,12). Investigators in this country carried out the first controlled studies of the efficacy and feasibility of continuous subcutaneous infusion therapy with insulin (13), making use of paired comparisons in volunteers with type 1 diabetes. These studies were followed by participation in multi-centre randomized trials, which have done much to establish the feasibility of large scale studies designed to examine the effects of conventional and experimental therapies on the complications of diabetes (14,15). These events have culminated in the development of the "Diabetes Control and Complications Trial", organized and supported by the National Institutes of Health in the United States (16). This study, addressing the possible effects of intensive control of blood glucose in type 1 diabetes mellitus, is being carried out in twenty-one centres in North America, with Canadian representation in two university clinics. The study is in its feasibility stage, and it will be determined later this year whether expansion and continuation of the trial through a period up to ten years is to be carried out. This study is a most formidable undertaking, in its demands on the volunteer subjects, in the difficulties of execution, and in terms of the financial cost. If it can be completed successfully, the results will be of the greatest importance, as discussed further below.

Contemporary Assessment of the Results of Intensified Insulin Therapy

Meanwhile documentation of the results of intensive replacement treatment with insulin in management of insulin-dependent diabetes mellitus has led to a number of conclusions, as reviewed in detail elsewhere (17,18). It appears that the attainable control of metabolism is systematically superior to that resulting from conventional therapy, but that established microvascular complications (manifested as retinopathy and nephropathy) are not systematically arrested, let alone reversed. The experience also suggests that the risks of intensive therapies, using infusion pumps or multiple insulin injections, are not obviously greater than those associated with conventional therapy. The total daily dosage with insulin and the prevailing levels of insulin in the blood are not in the mean greater with intensive therapies. It appears that no risks or factors that need inhibit continuing study with these methods have come to light. However, while the intensive therapies may be viewed as clinical options for consideration in individual subjects in accordance with the general approach to management of diabetes mellitus, it is not likely under these conditions that the provision of the facilities, equipment and personnel necessary for their more general application will be undertaken until firm conclusions regarding their potential benefits can be drawn.

Intensive Control of Glycemia in Non-insulin-dependent Diabetes Mellitus

With regard to the control of metabolism in non-insulin-dependent diabetes mellitus, the general strategy applying to IDDM has also been adopted, with similarly "compromised" targets for control (19). The role of the oral hypoglycemic agents as second-line treatment after establishment of diet therapy will be addressed as a specific topic at this workshop. There is evidence from clinical studies of intensive insulin therapy in subjects with persisting endogenous secretion of insulin who are classed as "NID but insulin-requiring", that administration of insulin according to strict but relatively simple treatment regimens can be highly effective in this group of patients (20). Demonstration of benefit from improved glycemic control in type 2 diabetes mellitus in terms of reduced morbidity of the disease would have an enormous impact on the management of this condition, as further discussed below.

Thus, with regard to the use of conventional methods of treatment in diabetes mellitus at the present time, it may be said that while there appears to be broad agreement regarding the objectives of control in metabolic terms, it is also clear that there is a great diversity in the application of therapies. While there is the prospect that the results of ongoing clinical trials will provide a basis for judgements regarding the indications for more strict control of metabolism, it is likely that these results will be delayed for some years, and it is of course not certain that clear-cut answers will be forthcoming.

New and Experimental Therapies in Diabetes Mellitus: Implications for the Clinical Care System

In recent years, studies of the etiopathology of diabetes mellitus have provided prospects of improved techniques for management, and of preventive therapies that may improve the prognosis and may even be capable of effectively curing the disease. These developments imply imminent challenges to the capacity of the health care system to provide the means for clinical assessment of the therapies, and to provide for their appropriate application in those cases where they prove to be effective. Thus research and development cannot be clearly separated from the clinical dimension, and the rate of progress is such that assessment of the implications of current investigations cannot be deferred.

In the practical sphere it is necessary to consider the consequences that would follow demonstration that more intensive control of metabolism in diabetes mellitus is mandatory in large groups of patients. As discussed earlier, it is possible that within the next few years it will be necessary to recommend optimal control of intermmediary metabolism from early stages of the disease, in order to anticipate and prevent the development of microvascular, macrovascular and neuropathic complications. The advent of the present policy of relative optimization of control in recent years has led to piecemeal exploration of these problems, with important initiatives from the Canadian Diabetes Association, and from provincial and federal agencies in some areas. However, these responses have been far from uniform, and must be rationalized.

Even greater strains upon the existing system will be forthcoming if any of the new experimental clinical approaches to the management of diabetes have to be applied in the clinical setting. These experimental approaches now include therapeutic or preventive regimens modulating the immune response based on current testing of the autoimmune hypothesis for type 1 diabetes mellitus, transplants of whole pancreas or preparations of pancreatic endocrine tissues, and use of mechanical devices for replacement treatment with insulin.

Prospects for Immunomodulatory Therapy

Recent studies based on the autoimmune hypothesis for B-cell destruction in type 1 diabetes mellitus have yielded encouraging results, suggesting that immunosuppression may enhance and prolong the spontaneous recovery of endogenous secretion of insulin that commonly occurs in the early months after diagnosis in type 1 diabetes (21,22). The plausibility of benefit from such therapies depends on the possible effects of maintenance of biologically significant levels of insulin secretion. The Canadian pilot study with cyclosporin in type 1 diabetes yielded results that led to the development of randomized controlled trials. Such a trial has been initiated by the Canadian/European Study group, involving seven centres in Canada and five in Europe, and funded in Canada by the Canadian Medical Research Council. Concurrently, randomized trials of the same intervention have been initiated or planned in France, Miami, Denver and Boston. It is likely that the short-term effects of administration of cyclosporin and other immunosuppressive treatments will be determined within the next one or two years. While confirmation would not constitute proof of longer-term clinical benefit, there would immediately arise the need to decide the place of such therapy in clinical management. The drugs in question are presumably only the first of many agents to be tested, and the approach constitutes only one among a number of possible immunomodulatory interventions to be considered. Furthermore, the results of this approach will help to determine the feasibility and importance of undertaking studies in identifiable high-risk groups of patients in the prodromal or preclinical phase of diabetes. This is not the place to discuss details of the formidable problem of identification of the appropriate groups of patients. However, it is clear that substantial progress has been made and that this question would have to be explored urgently on confirmation of a potentially beneficial effect of immunosuppression on insulin secretion in overt type 1 diabetes mellitus. Fortunately an established network of laboratories is providing monitoring of the immune response and the effects of immunosuppressive drugs in the Canadian clinical trial with cyclosporin. This structure could be expanded to cope with the increased demand that might come with more general applications in newly diagnosed type 1 diabetes. A rational and minimal immediate response would be to provide for the training of a cadre of clinical diabetologists who might take part in the evolution of this work. These trainees could be recruited to a program making use of expertise now available in several centres in this country, offering experience of the range of new techniques of diabetes care in their developmental stages, and providing for their dissemination when appropriate.

Transplantation of Insulin-Producing Tissues in Diabetes Mellitus

In parallel with studies related to the autoimmune hypothesis, and over a somewhat longer time period, various techniques for transplantation of pancreatic endocrine tissues have been developed. Recent and striking evidence obtained in the pancreas transplantation experience in type 1 diabetes suggests that autoimmune rejection of B-cells is likely to be repeated when the antigenic tissue is introduced in the subject who has already developed an immune response to B-cells (23). This became apparent in the experience of transplantation between identical twins, and illustrates a further situation in which immunomodulation in management of the autoimmune process (as opposed to pharmacological control of the generalized tissue rejection process), has become an integral part of the problem. Nevertheless, therapeutic experiments with whole pancreas transplants, with isolated adult islets, and with fetal endocrine pancreas, have been or soon will be initiated, with and without concurrent immunosuppression. In the case of transplantation of whole pancreas tissues, progress has been such that in some centres pancreas transplantation is considered as a clinical option when kidney transplantation is undertaken in treatment of end-stage renal failure in diabetes (24). Contrary to the expectations of only a few years ago, it appears that limitation of development of this approach to management may soon depend on the restricted availability of donor tissue, rather than on the efficacy or availability of the procedure. These problems will soon have to be addressed in this country, where experimental pancreas transplantation has been undertaken only on a very small scale to date.

Mechanical Devices for Replacement Treatment with Insulin

The results of studies with the so-called open-loop systems for continuous delivery of insulin discussed above have been impressive, and have provided the means for empirical assessment of the longer-term effects of the levels of metabolic control thus attainable on the complications of diabetes (17). These developments have also led to experimental studies with implantable devices for delivery of insulin. The effects of these devices are likely to be similar to those of external portable pumps, although the potential for delivery of insulin by means of the physiologic portal route, either by direct vascular access or through absorption of insulin from the peritoneal cavity may constitute an important advantage. Nevertheless the development of such devices has progressed at a modest rate, due to the problems with the formulation of insulin for use in such systems. While the place of this approach to therapy in the long-run remains to be determined, it is likely that major efforts to take advantage of these methodological advances will be made if it can be shown that intensive insulin therapy reduces the risks associated with diabetes. The provision of such treatment to appropriately selected patients on a generalized basis would present major problems for the existing health care system.

Experimental Therapies in Non-insulin-dependent Diabetes Mellitus

If it proves that optimization of metabolic control can ameliorate the complications of diabetes mellitus, and if similar evidence becomes available with respect to NIDDM (or if the judgement is made that such a conclusion may reasonably be generalized to include that condition) the enormous logistical problem of intensification of metabolic control in type 2 diabetes will have to be faced. As discussed above, intensive control with exogenous insulin can be very effective in type 2 diabetes mellitus. There is also a renewal of interest in the possible benefits of early intervention in non-insulin-dependent diabetes, particularly in relation to the effects of the oral hypoglycemic agents. While the mode of action of these agents remains unclear, and may depend on direct effects at the level of the target organ and on effects mediated directly or indirectly through enhancement of insulin secretion, it has recently been suggested that this approach to therapy in the so-called "chemical" phase of type 2 diabetes can reverse the thickening of the basement membrane in muscle (25). It remains to be determined whether such an effect is associated with clinical benefit to the integrity of those organs more critically affected in long-term diabetes, but it is clear that this question will have to be addressed in clinical investigation, and might lead to more generalized use in therapy.

In view of the discouraging level of compliance with therapeutic advice in type 2 diabetes, it is at least possible that approaches to the treatment of this condition in which the patient plays a relatively passive role, (such as by means of implantation of insulin delivery systems, or even by pancreas transplantation,) may have to be considered in selected groups among this very large number of patients.

Special Problems in the Management of Complications of Diabetes Mellitus

Major advances have been made in recent years in the management of renal failure and retinopathy as complications of diabetes mellitus. The discouraging results of kidney transplantation in end-stage diabetic nephropathy in the early years of this experience have been reversed, and it is now clear that this is the treatment of choice in that situation. In this context, as in others in which organ transplantation can be effective, it is urgently necessary to address the question of availability of the organs. The problem is potentially soluble if changes in the responses of the medical profession and the public can be effected (26). It is clear that the trend will be for performance of an increasing number of kidney transplants in management of diabetic nephropathy, adding to the manifest present stress on that clinical service.

Major advances in the management of diabetic retinopathy have also occurred in recent years, and it can be expected that a substantially smaller number of people with diabetic retinopathy will suffer complete blindness if the available techniques are applied at appropriate stages of the disease (27). In this context one limitation appears to be at the level of ascertainment of the need for the therapies. Appropriate frequency of assessment of the retina in people with diabetes was recommended in the special report on diabetes of the CDA (19). However, it is likely that these recommendations are not met in a substantial number of patients. This situation is remediable and should receive urgent attention. It has been suggested that the appropriate screening should be undertaken by ophthalmologists, rather than primary care physicians or retina specialists, but there are data suggesting that adequate use of such screening is not currently employed (28).

The Health Care Team in Management of Diabetes Mellitus

In this review it has repeatedly been necessary to refer to teams as well as facilities in relation to a number of problems. While this has been a recurring theme in discussions of the management of diabetes mellitus for many years, recent trends further emphasize the importance of these considerations. The contributions of several categories of medical specialists, of experts in dietary therapy, and of members of the nursing team with the skills necessary to therapy and monitoring of therapy, are essential. In addition, as has been apparent for several years, the education of people with diabetes and their families and other supporting persons, remains an outstanding problem in the management of the condition. As judged by objective assessments, the performance of the health care team in this regard has been far from satisfactory. This aspect of the clinical problem is the subject of a session at this workshop. It is clear that an important trend will be the allocation of resources to this area, with assessment of progress in attempts to improve the educational component essential to effective diabetes care.

Summary

The evolution of treatments used in management of diabetes mellitus in the clinical setting has been reviewed. Radical changes in management of diabetes will be called for, if the outcome of current investigations of intensified therapies replacement with insulin and of other experimental approaches in treatment suggests that these should be applied on a larger scale. These developments emphasize the importance of improving the capacity to monitor the effectiveness of the management of diabetes and to evaluate proposed new therapies in the clinical setting. This will call for expansion of the system in which such work can be undertaken in Canada. For this purpose systematic ascertainment of the disease and its complications is essential for management of the overall problem, and for quality control in respect of the efficacy of health care delivery in this context. The evidence cited, and the results of the detailed reviews of specific topics undertaken by the workshop on treatment of diabetes, also emphasize the importance of developing the health care team approach to management of this disease. These several considerations are reflected in the conclusions and recommendations of the workshop.

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DIET AS TREATMENT IN DIABETES MELLITUS

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Introduction

Diet is generally considered to be the cornerstone of all diabetes therapy (1) and the Canadian Diabetes Association, in concert with the American and British Associations believes that the importance of nutrition and diet in the management of diabetes cannot be over-emphasized (Table 1) (2,3).

However, in the past, diabetes diet therapy has been largely based on tradition, unsupported by clinical research (4). Recent work has suggested that the carbohydrate exchange lists that have been used for over three decades may not reflect the physiological effect of foods (5). In addition, at least two major types of diabetes have been identified, each requiring different dietary strategies. An even greater problem lies in convincing the patient to adhere to a prescribed diet.

The findings of the National Health Survey in America in 1968 (6) showed that 22% "were never given a diet for their diabetes", another 25% "had received a diet but did not follow it". Only 53% indicated they followed a prescribed diet. The situation in Britain appears to be similar (7). No such study has been carried out in Canada, so one must assume that the same situation exists here.

The time-consuming process of implementing diet as a meaningful treatment is not fully understood by the health care community, administrators, physicians and dietitians alike, and the knowledge and skills needed for diet counselling are largely unappreciated (8). Access to diet counselling is limited by availability and/or ability to pay. Assurance of the specialized knowledge and experience required by the dietitian, who prescribes and implements diet for the diabetic person is lacking.

Before we can describe the ideal dietary management of diabetes, let us first define exactly what we mean by "diet". According to Webster the noun DIET comes from the latin "diaeta", meaning "a prescribed dietary regimen" and the Greek "diaita", referring to "a manner of living". DIET is defined as "a prescribed .... allowance of food, especially when restricted in kind or quantity, as a health or punitive measure". With this definition in mind, it is not surprising that a diabetic diet is seen as punitive by many.

When we consider the therapeutic use of diet in diabetes, we must address at least five aspects of diet.

1. Composition of the ideal diabetic diet.
2. Dietary strategies to be used in different types of diabetes.

Table 1

Summary of Guidelines for the Nutritional Management of Diabetes Mellitus, revised by the National Nutrition Committee of the Canadian Diabetes Association, 1984 (2).

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1. Diet therapy is of fundamental importance in the management of diabetes mellitus.
2. Basic nutritional requirements are identical for diabetic and non-diabetic individuals.
3. Atherosclerosis is the major cause of death in diabetes, and diet therapy should be directed towards delaying its development.
4. Chronic hyperglycemia may contribute to the development of diabetic small vessel disease, and diet therapy should also be directed towards achieving blood glucose levels as close to normal as possible.
5. Increasing dietary carbohydrate by the use of starchy carbohydrates high in fibre can improve glucose tolerance, and will allow a decrease in dietary fat. Such factors may also contribute to a reduction in serum lipids.
6. The major dietary strategy in obese type 2 diabetes is reduction of body mass (weight).
7. The two major dietary strategies in type 1 diabetes are: 1) The co-ordination of insulin activity with food intake and exercise and 2) daily consistency in these three therapeutic measures.
8. Dietary compliance may be enhanced by education, individualization in the diet prescription, and adequate follow-up.
9. The ideal composition of a diabetic diet remains uncertain. Further clinical research is needed and we must be prepared to alter our approach to diet as new knowledge is acquired.

3. Prescription of the dietary regimen that will be ideal for a particular diabetic individual.
4. Implementation or diet counselling to ensure that the prescribed diet becomes part of that individual's lifelong way of eating.
5. Access to diabetes diet counselling.

Handing a patient a pre-printed diabetic diet sheet in the doctor's office or ten minutes before discharge would not seem to be the ideal way to alter lifelong eating habits (8,9,10). The use of pre-printed handout meal plans is discouraged (2,10,11,12) and an individualized approach to each patient is deemed desirable.

Composition of the ideal diabetic diet

Although the composition of the ideal diabetic diet remains largely unknown, the goals of such a diet can be clearly defined (2). The ideal diet:

a. would provide optimal nutrition throughout the life cycle of an individual.
b. would provide food energy appropriate for maintenance of energy levels and a desirable weight.
c. would promote normal glycemia.
d. would promote normal blood concentrations of cholesterol and triglyceride with the aim of preventing atherosclerosis and heart disease.
e. perhaps most important, would be attractive and acceptable to the person with diabetes, allowing a choice of foods that are affordable, available and easy to prepare.

In practice, a diabetic diet is defined by energy content and macronutrient composition which unfortunately does not assure the achievement of any of these goals.

It is assumed that the nutrient requirements of a person with diabetes are the same as they would be in the absence of diabetes but a review of available literature indicates that this assumption is not supported by data. Poorly controlled diabetes could be related to marginal stores of essential nutrients or trace elements. Even when deficiencies of iron, calcium or potassium have been diagnosed, this information is often not included when a referral is made for diet counselling.

Food energy requirements for persons with similar activity levels are known to differ greatly (13) and are difficult to estimate accurately even with calculations based on a food recall or diet diary (10). Even a desirable weight for someone with diabetes has never been defined. The widely used Metropolitan Life Insurance Height-Weight tables that correlate mortality with body weight are based on a population that deliberately excludes those with diabetes (14).

The ideal proportion of carbohydrate, protein and fat that will promote normal glycemia may vary with the type of diabetes and degree of control. Particular food combinations or meal composition may promote less excursion in postprandial glycemia in some persons (15). Different individuals vary in their metabolic response to different carbohydrate-containing foods (16).

Current dietary recommendations for decreasing the fat content of the diet are largely based on assumptions (17). Hypercholesterolemia is recognized as a major risk factor in coronary disease and a recent study demonstrated that decreasing elevated blood cholesterol levels significantly decreases the incidence of coronary heart disease. A diet high in saturated fat is associated with hypercholesterolemia (18). Atherosclerosis has been identified as the primary cause of death in type 2 Diabetes. The "prudent diet" recommends a decrease in the fat content of the diet to 35% or less of total energy even in the absence of hyperlipemia on the assumption that this will prevent atherosclerosis in the person with diabetes.

However, hyperglycemia and hyperinsulinemia may be more significant predisposing risk factors for atherosclerosis in type 1 and type 2 diabetes, especially when diabetes is poorly controlled (19). The fat content of a diabetic meal has traditionally not only provided satiety but also slows and prolongs the postprandial rise in blood sugar by delaying gastric emptying, thereby minimizing both hyperglycemia and hypoglycemia.

Whether atherosclerosis can best be avoided by severely limiting dietary fat in a normolipemic individual or by normalizing glycemia through more effective management of diabetes, or both, has yet to be determined.

Severely restricting the fat content of foods makes a diabetic diet unpalatable to many and is often more difficult to put into practice than is the restriction of sugar, especially for those who eat away from home a good deal.

Convenience foods are a labour-saving choice for many, yet most foods lack nutritional labelling indicating energy, sodium and macronutrient content that would enable the diabetic consumer to make an informed choice.

Fibre and complex carbohydrate have advantages in diabetic diet therapy (15,16,20) yet the nutrient data bank maintained by the Federal government gives only the total carbohydrate content of a food so that the amount of fibre and complex carbohydrate is not available to dietitians or those doing research.

Diabetic persons on low incomes or receiving social assistance find it difficult to buy the food necessary for adherence to the prescribed diet, and financial supplements available vary widely from province to province (21).

People in the growing ethnic community in Canada often do not have access to a dietitian who is familiar with traditional foods and their method of preparation (34).

Conclusion:

The goals of the ideal diet are easy to state; however the composition of this ideal diet remains uncertain. Much more research in areas of nutrition and food science is needed.

Dietary Strategies to be Used

Confusion in the dietary management of diabetes often arises from a lack of understanding of the differences between the two main types of diabetes and the dramatic differences in their dietary management (22). If diet is to be an effective form of treatment, goals for each person must be defined and their priority decided (8). Ideally, rather than prescribing energy content and macronutrient composition, a diabetic diet would be prescribed with a particular goal of treatment in mind, and the goals would vary with the kind of diabetes and other medical problems involved.

1. Type 1 Diabetes

In **type 1 diabetes,** the primary goal of dietary management is to encourage reasonable consistency regarding the time meals are eaten and the quantities of food ingested at each meal. The proportion of food energy derived from carbohydrate foods may vary as long as the diet is otherwise nutritionally sound (2,23).

Consistency is encouraged if the meal plan is based on the usual eating habits, activity pattern, work hours, family mealtimes and food preferences of the individual (8-10). It is essential tha the patient be involved in the prescription of the diet (9). The type and amount of insulin administered is then closely matched with the meal plan. If daily routine varies from workday to weekend, or from shift to shift, an appropriate meal plan and insulin regimen is prescribed for each variation.

Effectiveness of this insulin-food balance is best achieved when the educated person records self-monitored blood glucose values, and any variables affecting these values, and discusses them with his/her health care provider. Expensive hospitalization is not usually indicated in the absence of ketoacidosis. Ideally the person with diabetes would be educated thoroughly regarding the composition of foods and their impact on postprandial glycemia, the time-action curves and potency of the insulins prescribed, as well as an understanding of the effect of exercise. With self blood glucose monitoring and an appropriate insulin regimen, meal plans and insulin dosages can be adjusted to allow considerable variety in food selection without any sacrifice of excellent blood glucose control (10). Strict lipid modification would be implemented only when a need was indicated.

In practice, the person newly diagnosed with type 1 diabetes is admitted to hospital for ten days and an insulin regimen is prescribed, based on blood glucose values that reflect the ingestion of standard meals based on the hospital menu. Meals are eaten at times convenient to hospital routine, with the patient in bed or relatively inactive. There may be no discussion of the routine that will be followed after discharge. When the patient goes home, meal hours and insulin injection times must be changed to accommodate usual work or school routines or family preferences. Often the composition of hospital meals is difficult to maintain at home, especially if meals must be eaten at work or if ethnic foods are traditionally eaten. The person is usually more active as well and sufficient energy is often not provided by the hospital diet. The insulin regimen, established with such time-consuming detail and expense in hospital, no longer matches the person's exercise-meal pattern at home, and good control is no longer possible. Hyperglycemia alternates with hypoglycemia. Extra food is eaten to counteract the hypoglycemia, often resulting in unwanted weight gain, and another case of "patient non-compliance" is recorded.

2. Type 2 Diabetes: obese

Although the group of persons with type 2 diabetes is heterogeneous, and inappropriately elevated blood glucose concentration is generally common to all. Most are obese and over forty, although at least 20% of this group will be non-obese (10). Their diabetes is due to various combinations of insulin resistance and impaired insulin secretion, although never as severe as in type 1 diabetes. It is difficult to suggest a diet that is ideal for all.

In general, reduced food intake is considered the best treatment for obese persons with diabetes. Weight loss is associated with improvement in glycemic control in many cases and with a significant increase in insulin secretion in some (24). An improvement in blood glucose concentration often occurs with only a minimal reduction in body weight (25). The major problem is to motivate the patient to remain on an energy-restricted, nutritious diet and to maintain a reduced body weight. Consistency in energy or macronutrient intake is not crucial, nor is extra food needed for exercise or for prevention of hypoglycemia. Even the complete avoidance of refined sugars is not necessary (26).

The ideal approach to type 2 diabetes with obesity would be to emphasize the value of a nutritious healthy diet, and to teach the obese person the composition and calorie content of foods so that choices made are informed ones (10). Small changes in eating and exercise behaviour would be encouraged and progress followed closely until weight loss and/or improved diabetic control is established. Self-monitoring of blood or urine glucose would provide continued motivation. Psychotherapy would be prescribed if overeating has an emotional basis. Only permanent changes in eating behaviour will ensure that diet alone is an effective form of treatment. Oral medications and insulin therapy would not be initiated until the educated patient has tried diet alone for a period of time. If symptoms are acute at the time of diagnosis, a carefully supervised period of semi-fasting might decrease insulin resistance and improve diabetes dramatically, making more aggressive management unnecessary (27). Such an approach has proved to be not only cost-effective but effective in reducing complications as well (28). The use of insulin therapy in the already insulin-resistant obese individual is debatable.

In reality, the obese person with diabetes is often given a diet sheet outlining a severely energy-restricted diet and only when failure to lose weight has been demonstrated, or escalating amounts of insulin or oral agents are accompanied by weight gain, is the patient referred for intensive dietary instruction. It appears that considerable money is being wasted in health care delivery for those with obesity-induced diabetes when oral agent and/or insulin therapy is substituted for appropriate nutritional education and follow-up by a dietitian (28).

3. Type 2 Diabetes: non-obese

The ideal dietary regimen for the non-obese person with type 2 diabetes is less clear and still controversial. Persons with mild diabetes who can still secrete significant amounts of insulin have benefited from a diet high in starchy carbohydrate (CHO) and leguminous fibre (29). In other type 2 patients, a high CHO, low fat diet causes a worsening of diabetic control (30), probably related to a more limited capacity to secrete insulin. A low carbohydrate, higher fat diet may promote normal glycemia and minimal cardiovascular risk in the older person, especially if hypertriglyceridemia is a problem as well (17).

Therefore, to use diet as an effective treatment in non-obese type 2 diabetes, it is essential to tailor the dietary strategy to the individual. Cholesterol and triglyceride concentrations would be measured. Assay of insulin concentration or C-peptide excretion would determine the availability of endogenous insulin. This information would be readily available to the person devising the appropriate dietary strategy. The diabetic person would be educated and taught how to monitor blood glucose before and after meals so that effectiveness of diet therapy could be assessed. Further manipulations of diet and exercise might be necessary until adequate control is established on diet alone. Oral medication would be added to the dietary treatment only if satisfactory control could not be established. Self monitoring would indicate when endogenous insulin supply is insufficient and would signal the need for insulin therapy.

4. Diabetes and Growth

When diabetes occurs concurrently with changing growth needs, the primary goal of diet therapy will be to ensure that the increased nutrient and energy requirements of this growth period are met. Examples would be a growing child, or a person with type 1 diabetes who becomes pregnant, or a pregnant woman who develops gestational diabetes. In order to ensure normal growth and development, diabetes must be carefully managed, using the same strategies as outlined for type 1 or type 2 diabetes. Growth needs should be reassessed at regular intervals (every six months in the child; or during each trimester of pregnancy) and meal plans should be adjusted accordingly, recognizing that a change in diet might change insulin requirements. Preconception nutrition counselling would ideally precede each planned pregnancy.

Too frequently, in practice, a child is given a diet at the time of diagnosis that is appropriate to growth needs at that particular age. Several years later, there will have been no change in prescribed diet despite changing energy needs. Either the young person will have abandoned any attempt to follow the irrelevant prescribed dietary regimen, or, if followed, energy intake will now be in excess of changed growth needs and unwanted weight gain will have occurred. In either situation the poor glycemic and/or weight control is once again identified as "patient non-compliance".

The importance of diet in the management of a pregnancy complicated by diabetes is increasingly being recognized and preconception counselling is the norm in some high risk centres. However, too often the energy demands of pregnancy are underestimated (31) or the potential macrosomia of the infant is mistakenly attributed by the family physician to maternal weight gain rather than maternal hyperglycemia (32). Sufficient protein is needed for cellular growth and replication. If total energy is too restricted, dietary protein will be converted to energy and rapidly dividing cells may suffer (31).

Conclusions:

a. Diabetic diet should be prescribed according to desired outcome, considering the type of diabetes and other medical conditions.
b. Individualization is essential.
c. Self blood glucose monitoring increases effectiveness of diet.
d. Prescription of a dietary regimen is time-consuming and requires special skills and knowledge.

Prescription of the Diabetic Diet

Ideally, the prescription of a suitable regimen requires close cooperation between physician, dietitian and patient. The physician makes the initial diagnosis and defines treatment goals and medical priorities appropriate for the kind and degree of diabetes present, taking into consideration the past medical history and age of the patient. Appropriate laboratory tests are ordered to identify hyperlipidemias. Endogenous insulin supply is measured when appropriate. The patient is given basic information about diabetes and a diabetic way of eating and is referred to a dietitian, preferably located in the same hospital, clinic or office for further counselling as soon as possible.

The referral prescribes diabetic diet as treatment for the patient stating the physician's goals of treatment. For example, important goals of diabetic diet could be:

- to regain lost weight,
- to establish a consistent eating pattern on which to base appropriate insulin therapy
- to achieve a 5 kg. weight loss
- to maximize the endogenous insulin supply present with a high carbohydrate, high fibre diet
- to minimize demand on a limited endogenous insulin supply by distributing food intake over six small meals a day.

Other specific goals could be described as well, e.g. decrease sodium intake (with rationale); decrease hyperlipemia (giving most recent plasma cholesterol and triglyceride values). Cases of secondary diabetes due to pancreatitis or pancreatectomy would include details regarding pancreatic enzyme replacement (if any) and malabsorption (if present).

The ideal prescription would be dietary treatment, not by energy content and macronutrient composition, but by treatment goals to be achieved.

Implementation of Dietary Prescription (or diet counselling)

Theoretically, this can be carried out by an interested physician with a special interest in food and nutrition and the time and skill needed to take a detailed diet history and develop a meal plan (10). However, an interested physician would have to measure the cost-effectiveness of such an involvement. Alternately, a registered dietitian-nutritionist with a special interest in diabetes can work with the patient to develop an eating plan designed to achieve the goals of treatment outlined by the physician (11).

Diet therapy is most effective when based on a close interaction between diet counselor, individual patient and understanding physician. The patient needs to feel the united support of physician, diet counsellor and family if necessary dietary changes are to be made. This close interaction is imperative if blood glucose control is to be achieved in patients receiving insulin (10).

Prescribing a dietary regimen or meal plan for the diabetic person to follow, and carrying out the diet counselling needed to make it effective, requires both knowledge and time. The knowledge and skills required have been outlined by the National Nutrition Committee of the Canadian Diabetes Association (33) (Table 2). This knowledge must be acquired at university or during internship and must be kept up-to-date through continuing education. Effective diet counselling is time-consuming. It is estimated that it takes 6 to 12 hours of concentrated effort to properly evaluate and educate a patient about diet (9), ideally divided into several 15 to 20 minute visits (10). Some of this education can take place in a group setting but much must be carried out in one-to one counselling sessions since eating habits and treatment goals differ greatly between individuals. If the responsibility for meal planning and food preparation is shared with or assumed by someone other than the patient, it is important that this person participate in counselling as well or there is little chance that the meal plan will be followed (9).

An individualized approach is essential if diet is to be an effective form of treatment (2,8-12). The challenge to the dietitian is to help each individual client learn to live with diabetes within a chosen lifestyle, recognizing that lifestyle itself changes with season, growth and changing interests. The patient is an important participant in this process (9). The eating plan must be developed in close cooperation with the person who has to live with it. The dietitian encourages only changes in eating habits that are necessary for nutritional well being and adequate diabetic control, recognizing that changing behaviour is difficult. Dietary strategies are carefully planned in consultation with the physician so that treatment goals are achieved.

New diet counselling strategies are being tested and evaluated by dietitians that incorporate the approach of the sociological health belief model with a psychological approach and a step-by-step approach to education (35). This individualized approach to diet counselling involves four stages:

1. Assessment of patient's complaints and requests as well as health beliefs, using open-ending questioning and effective responses to encourage the patient to talk openly and honestly.

2. Assessment of present knowledge and skills of patient, and significant others involved, and the progressive development of meal planning skills needed for (a) survival, (b) home management and (c) lifestyle improvement.

3. Setting of realistic short term and long term treatment goals, after negotiating a consensus of the therapy goals of patient and family, dietitian and physician.

4. Continuous monitoring and evaluation of progress toward short-term and, in some cases, long term goals, giving additional education and developing additional skills as needed.

Table 2

Knowledge Required by the Dietitian/Nutritionist Counselling the Person with Diabetes
National Nutrition Committee, Canadian Diabetes Association - 1977 (33)

A background knowledge in:

1. Applied science such as biochemistry, physiology, food chemistry and normal and therapeutic nutrition.
2. Social sciences such as psychology and sociology.
3. Ethnic foods and eating habits.

Further background acquired during dietetic internship or a programme of continuing education:

1. Interviewing techniques which enable assessment of the patient's or client's lifestyle.
2. Knowledge of insulin and oral hypoglycemic medications.
   - 2.1 Types currently in use
   - 2.2 Physiological action
   - 2.3 Timing of release
   - 2.4 Interaction with activity, stress, obesity
   - 2.5 Basic appreciation of interaction with other drugs.
3. Knowledge of hypoglycemia and hyperglycemia: symptoms, treatment and prevention.
   - 3.1 Relation of both to diabetic complications and patient discomfort
   - 3.2 Methods of measurement and their interpretation
   - 3.3 Prevention of both conditions by meal planning, use of snacks and compensation for activity
4. Knowledge of Meal Planning
   - 4.1 Ensure nutritional adequacy of food plan for individual
   - 4.2 Use of exchanges or a simplified approach in planning dietary guidelines adapted to the individual's needs
   - 4.3 Conversion of household recipes to exchanges
   - 4.4 Energy needs (kilocalories or kilojoules)
     1. How to assess
     2. How to prescribe
   - 4.5 Current thinking as to optimal carbohydrate and lipid levels
5. Role of Dietitian/Nutritionist in metabolic assessment and regulation of diabetes mellitus.
   - 5.1 Use dietary history as basis of meal planning
   - 5.2 Understand the need for a constant intake of carbohydrate during metabolic assessment
6. Knowledge of adjustment of meal plan according to special situations (e.g. pregnancy, sickness, growth, aging)
   - 6.1 Adjustment of carbohydrate and/or insulin for extra activity (notify physician in latter case)
   - 6.2 Adjustment of the amount and distribution of carbohydrate to prevent or correct starvation ketosis during pregnancy
   - 6.3 Adjustment of meal time or type of insulin to suit individual's life style (e.g. commuting, shift work).

Table 2 (continued)

7. Team Approach - Role of the Dietitian/Nutritionist
    7.1 Initiate communication to the physician when need for adjustment of insulin dose or type is identified
    7.2 Communicate to physician dietary changes which are being made
    7.3 Communicate to nurse(s) the importance of snacks
    7.4 Communicate to appropriate member of the teaching team the need for reinforcement of teaching.

In practice, this ideal is seldom achieved. Few medical schools teach nutrition and diet therapy and behaviour modification in a meaningful way either on campus or during internship. Dietitians may not have the opportunity to develop a specialized knowledge of diabetes therapy either at university or during their year of internship in a teaching hospital. Furthermore, there is no recognized means to identify the dietitian-nutritionist who does have this knowledge.

Access to Diabetic Diet Counselling

An even greater problem is access to diabetic diet counselling. The majority (70%) of dietitians in Canada are employed by institutions and only 30% describe themselves as clinical or therapeutic dietitians (36). With current government budget restraints, hospitals are often understaffed. Most hospital out-patient diet counselling services have waiting lists and are usually available only to patients of hospital medical staff.

The Canadian Dietetic Association has 3,700 active members in nine provinces (excluding Quebec), with 1,500 of these employed in Ontario alone. The Quebec Dietetic Corporation has approximately 600 members. Only 500 dietitians in Ontario classify themselves as clinical or therapeutic dietitians, and many of these may have administrative duties as well (36). The Professional Health Workers Section of the Canadian Diabetes Association lists 300 dietitians in Canada as active members, indicating a special interest in diabetes. Membership by provinces is shown in Table 3.

Many registered dietitian-nutritionists would like to be in private practice. However nutrition counselling is an insured service only when carried out by a physician. Diet counselling carried out by a registered dietitian-nutritionist is not covered by goverment medical insurance in any of the nine provinces surveyed. Access to private diet counselling is thus limited by the patient's ability and willingness to pay. Most patients feel that since diet is such an important part of their diabetes treatment, they should not have to pay for diet counselling out of their own pockets. Thus, many wait until an out-patient appointment is available or do without. It is estimated that a total of 19 registered dietitians are in private practice in

Table 3

Dietitian Members of Professional Health Workers Section, CDA in 1985

Newfoundland	13
Nova Scotia	29
New Brunwick	15
Prince Edward Island	1
Quebec	9
Ontario	113
Manitoba	26
Saskatchewan	23
Alberta	54
British Columbia	36
	319

Canada excluding Quebec (37). Access to diabetic diet counselling is limited at the institutional level by staffing and budget restraints, and at the community level by lack of insurance coverage for diet counselling. All these factors are controlled by provincial government. There is no shortage of dietitians in Canada although certain geographical areas may lack the services of a qualified dietitian, just as they may lack a physician's services. The shortage lies in the number of dietetic internships available and the number of positions for dietitians available in government-funded institutions.

In 1984, five Ontario universities offering courses approved by the Canadian Dietetic Association graduated 145 potential dietitians, each with a B.Sc. degree and a major in foods and nutrition and a professed interest in dietetics as a profession (36). Out of these 145 graduates, 86 met the curriculum requirements for concentration A (Clinical Nutrition) (Table 4,5) and 68 met the requirements for concentration B (General Dietetics) (Table 4,5). However, only 80 of these 144 Ontario graduates were able to obtain a dietetic internship in an accredited Ontario teaching hospital. Without this supervised dietetic internship in a clinical setting, a university graduate is unable to obtain a position in an accredited hospital of any size, so the supply of dietitians is effectively controlled by the number of dietetic internships available, which is determined by the provincial government.

In Quebec the situation is somewhat different. Dietetic internship is integrated with undergraduate studies so that the graduating dietitian is already eligible for professional certification and practice. Approximately 59 dietitians are in private practice in Quebec (38).

TABLE 4

THE CANADIAN DIETETIC ASSOCIATION

ACADEMIC REQUIREMENTS
for Membership or Internship

A bachelor's degree from a University whose accreditation is acceptable to the Canadian Dietetic Association and contains or is supplemented by the following credits:

CORE SUBJECTS
39 credit hours - basic minimum
All core subjects required

HUMANITIES AND SOCIAL SCIENCES....12	NATURAL SCIENCES....9		PROFESSIONAL SUBJECTS..................18	
	General Chemistry	3)	Foods - Basic	3)
	Organic Chemistry	3)	- Advanced	3)
	Microbiology	3)	Basic Human Nutrition	6)
			Basic Principles of Management	3)
			Communication Arts	3)

CONCENTRATIONS
Choice of A, B, C, or D - Underlined subjects or subject areas are required.

A	B	C	D
CLINICAL NUTRITION - 27 HUMAN NUTRITION - 9 Advanced Clinical SUPPORTING SCIENCES - 18 Biochemistry (Physiology (12 Advanced Biochemistry Advanced Biology Advanced Physiology Anatomy Clinical Biochemistry Computers Pathology Pharmacology Statistics	GENERAL DIETETICS - 27 HUMAN NUTRITION - 6 Advanced Clinical FOODSERVICE SYSTEMS MANAGEMENT - 9 Foodservice Systems Organization and Management Quantity Food Production Management Foodservice Facilities Cost Control and Accounting Personnel SUPPORTING SCIENCES - 12 Biochemistry (Physiology (9 At least one of: Computers (Mathematics (3 Statistics (	FOODSERVICE SYSTEMS MANAGEMENT - 27 FOODSERVICE SYSTEMS MANAGEMENT - 9 Foodservice Systems Organization and Management Foodservice Facilities Quantity Food Production Management MANAGEMENT - 9 Advanced Management Theory Cost Control and Accounting Personnel Business Law SUPPORTING SCIENCES - 9 Advanced Social Sciences Computers Mathematics Statistics	COMMUNITY NUTRITION - 27 HUMAN NUTRITION - 9 Advanced Community Clinical FOODSERVICE SYSTEMS MANAGEMENT - 3 Foodservice Systems Organization and Management SOCIAL SCIENCES/EDUCATION - 6 Program Planning & Education Theory Research Methods Community Organization SUPPORTING SCIENCES - 9 Biochemistry Physiology Advanced Social Sciences Computers Statistics

1 lecture hour or 2 laboratory hours per week for 1 half year is counted as 1 C.D.A. credit. These do not coincide with the course credits outlined in university calendars.

Table 5
SECTION 2 - PROGRAMS IN CANADA

Concentrations in Dietetic Internship Programs offered in Canada

Internship programs provide experiences to develop basic competencies required by all dietitians and more specialized competencies in preparation for specific roles in the dietetic profession. These specialized competencies are expressed through the concentration of the internship program. Programs are offered with emphasis in clinical dietetics, general dietetics and administrative dietetics. A program with concentration in community dietetics is in the developmental stage.

Clinical Dietetics Program - Concentration A

A clinical dietetics internship program provides the intern with experiences which emphasize:

i) developing and implementing a nutrition care plan based on nutrition assessment and correlated with other aspects of health care in a variety of clinical settings. (Wenberg, 1977, p.52);
ii) counselling clients/patients individually and in groups about nutrition principles, the selection and preparation of foods, and related topics within the context of their social, psychological, cultural and economic environment (Wenberg, 1977, p.52);
iii) participating as a health care team member, responsible for evaluating, improving and maintaining the nutritional status of the patient;
iv) applying the principles of management to the administration of clinical services of the dietetics department;
v) applying communication and education principles and current research results to improve the quality of clinical nutrition services.

This program prepares the graduate intern to function as an entry-level dietitian in a clinical setting which may provide specialized care, e.g. medical, surgical, pediatric, oncology.

Dietetic Internship Programs: Procedures Manual, The Canadian Dietetic Association, 1983

General Dietetics Program - Concentration B

A general dietetics internship program provides the dietetic intern with experience primarily in two areas of dietetics: clinical nutrition and foodservice administration. There is flexibility in the general program through electives, projects, and assignments to provide focus on a chosen area of dietetics. The intern's experiences include:

i) developing and implementing a nutrition care plan based on nutrition assessment and correlated with other aspects of health care (Wenberg, 1977, p.52);
ii) counselling clients/patients, individually and in groups about nutrition principles, the selection and preparation of foods and related topics within the context of their social, psychological, cultural and economic environment. (Wenberg, 1977. p.52);
iii) participating as a health care team member, responsible for evaluating, improving, and maintaining the nutrition status of the patient;
iv) applying skills in financial, personnel, material, and facility management with the principles of nutrition to the development, administration, and evaluation of foodservice systems;
v) applying communication and education principles and current research results to improve the quality of foodservice administration and clinical nutrition services;
vi) establishing and maintaining high standards of quality, safety, and sanitation in all aspects of nutrition care.

The general program prepares the graduate intern to function in an administrative and/or clinical capacity in a small institution or entry-level position in a larger institution.

Internship Manual, Canadian Dietetic Association, 1985

The Clinical Dietetics internship program (Table 5) prepares the graduate to function in a clinical setting which may provide specialized care. There are 28 such internships available in Canada each year; 19 of these are in Ontario hospitals, 6 are in Manitoba and 3 positions are offered in Alberta. These would be the internship programs which could be expected to provide potential specialists in diabetes diet therapy, keeping in mind that diabetes is only one of several clinical conditions requiring specialized nutritional care.

The General Dietetic internship program (Table 5) prepares the graduate to function in an administrative and/or clinical capacity in a small institution or an entry-level position in a larger hospital. In

Canada (excluding Quebec), 152 General Dietetic internships are available in 1985 (60 of these in Ontario). In addition, 8 Community Nutrition internships were available (concentration D - Table 4), 6 in Manitoba and 2 in Ontario.

There is often confusion as to the difference between a dietitian and a nutritionist. By definition, a clinical dietitian is a specialized dietetic professional who affects the nutritional care of individuals and groups in health and illness. As a member of the health care team, the clinical dietitian provides nutrition assessment, planning, implementation (including education and referral) and evaluation services. A general dietitian provides similar services at a less specialized level and serves in an administrative capacity as well. The community dietitian-nutritionist often has a graduate degree (M.Sc.) in nutrition as well and works in a community setting, affecting the nutritional care of individuals and groups in health and illness, but with a major focus on health promotion.

Graduate interns from Clinical, General or Community Nutrition internships are all qualified to provide diet counselling in health and illness. Knowledge of diabetes and clinical experience with diabetes vary with the university and teaching hospitals. If more internship positions in both A and B concentrations, as well as the opportunity to acquire further knowledge about diet as treatment in diabetes, were available, there would be ample qualified dietitians to provide treatment to the diabetic population of Canada in urban settings both large and small. Access to these dietitians, however, is dependent on government funding.

Conclusions:

1. More nutrition-related research is needed before the composition of the ideal diabetic diet can be defined. The kind and amount of certain foods eaten during a metabolic study can introduce variability unrelated to macronutrient composition of diet.
2. Appropriate and effective dietary strategies differ according to the type of diabetes. Further clinical research is needed to define these strategies, and to provide markers that will clearly distinguish the type and degree of diabetes so that dietary treatment can be planned more effectively.
3. Most physicians lack the time and/or the specialized knowledge and skills required for effective diet counselling.
4. Many dietitians do not have the specialized knowledge of diabetes and diet therapy required to counsel those with type 1 and type 2 non-obese diabetes.
5. Dietitians with a specialized knowledge of diabetes exist but there is no recognized means of identifying them at present.
6. The number of dietitians available to carry out effective in-patient counselling is insufficient in many hospitals due to departmental priorities and/or budget constraints.

7. Out-patient diet counselling services often restrict access to patients of staff physicians and may have lengthy waiting lists. There is no guarantee that the dietitian is qualified to give the specialized counselling required in certain types of diabetes. Time and staff for follow-up is often lacking.
8. Patients may not have access to any registered dietitian because of their geographical location in Canada.
9. Access to dietitians in private practice is limited by the patient's ability and willingness to pay since diabetic diet counselling is not covered as a government insured service in any of the provinces. Many consulting dietitians are specialized in diabetes counselling but certification is needed.

Recommendations to ensure effective use of diet in the treatment of diabetes in Canada.

1. Fund research in Canada to determine effective dietary strategies and food combinations that will promote normal glycemia and lipemia in different types of diabetes.
2. Require that all metabolic and clinical research funded by CDA/JDF provide adequate information about diet and food administered during study.
3. Ensure that university curricula provide both medical and dietetic students with an understanding of the important role of diet in the treatment of diabetes and of their role in its effective application.
4. Provide interns, both medical and dietetic, with clinical experience that demonstrates the individualized planning and implementation of appropriate dietary strategies for different types of diabetes, with the opportunity to observe physicians and dietitians working in close cooperation.
5. Encourage competency in diabetes diet counselling through continuing education, specialized internship programs, and specific professional certification.
6. Designate Diabetes Training Centres in Canada that would integrate university and teaching hospital facilities and would provide specialized training for family physicians and dietitians as well as diabetes nurse educators.
7. Encourage provincial Ministries of Health to include diet counselling as an insured service when carried out by a registered dietitian-nutritionist, in cooperation with a registered physician. This would make access to diet counselling independent of institutional budgets. Encouraging physicians in private practice to use the services of such a registered dietitian-nutritionist would ease the load on the often over-extended out-patient facilities. The time needed for effective diabetic diet counselling should be considered when fee for service is established.

8. Require nutritional labelling on food products that describes energy, macronutrient and sodium content so that diabetic persons can eat a wide variety of foods and yet maintain consistency in meal content and make informed choices of foods that are lower in fat and sodium content.
9. Provide a nutrient data bank that states total carbohydrate content as starch, sugar and fibre, so that the type of carbohydrate associated with the least glycemic effect can be readily identified in the Canadian food supply.

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THE USE OF ORAL HYPOGLYCEMIC AGENTS IN THE TREATMENT OF DIABETES MELLITUS

George Fantus, M.D.

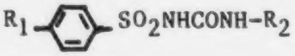
The possibility that an orally effective "insulin" or "insulin-like" drug could be used for the treatment of diabetes mellitus in order to avoid daily injections of insulin has attracted the attention of basic scientists, clinicians and patients for many years. At this time no such ideal replacement for insulin is available. However, two categories of oral hypoglycemic agents are being extensively used in Canada for the treatment of type 2 or noninsulin-dependent diabetes mellitus (NIDDM) formerly referred to as adult-onset or ketosis-resistant diabetes mellitus. Before considering details regarding the appropriate use of these agents, a brief description of these drugs and their mechanisms of action is presented.

One group of agents are referred to as the sulfonylureas. As illustrated in Fig. 1 these agents have in common a central structure with variable groups attached at either end (1,2). The discovery of the hypoglycemic effects of these compounds resulted from chance observations while investigating their potential as antibiotics (3). These agents are divided into first and second generation compounds which reflect their relative potency per unit weight as hypoglycemic agents and indicate the timing of their introduction for the treatment of NIDDM. It is beyond the scope of this report to discuss details of the metabolism, excretion, drug interactions and possible adverse effects of these agents. Certain aspects may be mentioned when relevant to the discussion. The reader is referred to several comprehensive reviews (1-5).

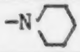
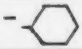
Of major relevance to the use of these agents is their mechanism of action. It was clear from early studies that insulin secretion is acutely stimulated by sulfonylurea administration (3,4). This effect on the B-cells was accompanied by the observation that in the absence of the pancreas these drugs were not effective in lowering blood glucose (6). After the introduction of sulfonylureas into clinical use and the development of the radioimmunoassay for insulin several studies showed that although insulin concentrations were acutely increased these gradually reverted to baseline or even lower while the patients' blood glucose concentrations remained well controlled (7,8). These data led to the hypothesis that these agents have insulin-like or insulin potentiating effects in the insulin target tissues. There are now a number of in vitro studies which suggest that there are such effects on liver and adipose tissue (9-14). The question of whether these effects are related to the changes in insulin receptors observed in subjects with NIDDM treated with sulfonylureas is not resolved (15,16). However, the bulk of recent data favors a postreceptor (postbinding) site of action (9-14). The conclusion that these agents have at least two sites of action, the pancreas and peripheral tissues, has led to the proposal of combining sulfonylurea therapy with insulin therapy. Such a study in subjects with type 1 or insulin-dependendent diabetes mellitus (IDDM)

Figure 1. THE STRUCTURES AND CLASSES OF VARIOUS SULFONYLUREAS

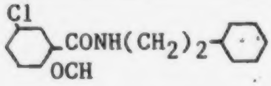
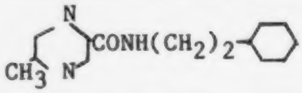
CENTRAL STRUCTURE


R_1
$SO_2NHCONH-R_2$

FIRST GENERATION COMPOUNDS

NAME	R_1	R_2
TOLBUTAMIDE	CH_3-	-$(CH_2)_3CH_3$
CHLORPROPAMIDE	C_1	$(CH_2)_2CH_3$
TOLAZAMIDE	CH_3	
ACETOHEXAMIDE	CH_3CO-	

SECOND GENERATION COMPOUNDS

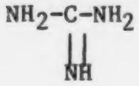
NAMW	R_1	R_2
GLYBURIDE	 Cl $CONH(CH_2)_2$ OCH	
GLIPIZIDE	 N $CONH(CH_2)_2$ CH_3 N	

showed that there were no changes in insulin receptors or insulin requirements to lower glucose (13). It is thus confirmed that use of these oral hypoglycemic agents should be confined to patients with NIDDM (type 2). Whether such combination therapy (insulin and sulfonylurea) is effective in NIDDM is not clear. There is evidence that insulin treatment also corrects to a significant extent the peripheral resistance in NIDDM (18). Whether the sulfonylurea drugs will correct residual defects in insulin action, i.e. not corrected by insulin treatment alone, which are unique to patients with NIDDM is a matter of conjecture.

The other group of oral hypoglycemic agents are the biguanides (Fig. 2). As early as 1918 guanidine was shown to have glucose lowering activity (19). Although this compound was toxic, renewed interest in oral treatment of diabetes led to the development of the biguanides, in the 1950's (16). At the present time only one biguanide, metformin, is available for clinical use in Canada and Europe (20). None is available in the United States. The reason for this is the unacceptably high incidence of morbidity and mortality caused by phenformin, the first biguanide introduced into the American market, because of lactic acidosis (21). On the other hand metformin, which is a smaller molecule and more rapidly excreted by the kidney, does not cause lactic acidosis unless administered to patients with renal failure in whom these agents are contraindicated (22). After 56,000 patient-years of monitoring in Canada from 1972-1983 there were no documented cases of lactic acidosis (23). This documentation of clinical safety if appropriately prescribed has allowed metformin to remain available for clinical use (20). The mechanism of action of metformin is not established (24). Many early studies of the mechanism of action of the biguanides used very high concentrations (much higher than serum levels) to document effects (20). Thus it has been demonstrated that (1) gastrointestinal glucose absorption is delayed and perhaps even partially blocked (25) (in this sense the drug mimics some of the effects of fiber), (2) hepatic gluconeogenesis is inhibited (26) and (3) oxidative phosphorylation in muscle is blocked leading to anaerobic metabolism (21). More recently effects on insulin receptors and insulin action have been demonstrated in vitro and in vivo (28-32). At the present time available evidence supports the view that effects on the gastrointestinal tract and an insulin-like effect on peripheral tissues both contribute to the glucose lowering effects of the drug. The relative contribution of each of these remains to be established. It is clear however that in contrast to the sulfonylureas there is no significant effect on insulin secretion. Furthermore the clinical observation that these two classes of agents may be combined with additive effects suggests that they have different mechanisms of action (19,31,33).

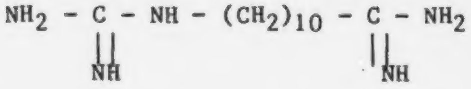
In an attempt to make recommendations regarding the use of oral hypoglycemic agents it is important to examine the evidence for their efficacy as well as for any toxicity. Also it is important to define a set of treatment objectives so that efficacy may be assessed with these

Figure 2. THE STRUCTURE AND ACTIVITY OF VARIOUS BIGUANIDES



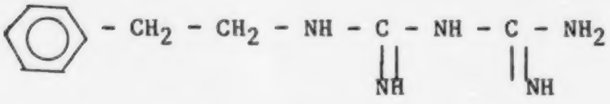
$NH_2-C(=NH)-NH_2$

Central structure = guanidine

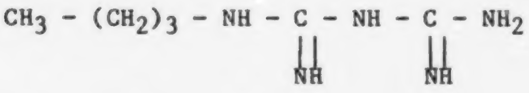


$NH_2-C(=NH)-NH-(CH_2)_{10}-C(=NH)-NH_2$

decamethylendiguanidine
Synthalin A; blood sugar lowering, hepatotoxic, induces lactic acidosis.

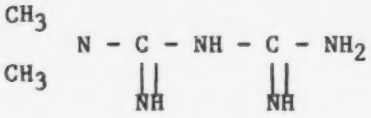


B-phenethylbiguanide
Phenformin, DBI, oral hypoglycemic, induces lactic acidosis



$CH_3-(CH_2)_3-NH-C(=NH)-NH-C(=NH)-NH_2$

n-butyl-biguanide
Buformin, oral hypoglycemic, induces lactic acidosis



$(CH_3)_2N-C(=NH)-NH-C(=NH)-NH_2$

N - 1, 1-dimethylbiguanide

Metformin, oral hypoglycemic, may induce lactic acidosis in the presence of renal failure end points in mind. As discussed above these drugs are used for the treatment of noninsulin-dependent diabetes. It has been documented that these patients are at risk for the development of the same microvascular complications, i.e. retinopathy and nephropathy as well as neuropathy as are patients with IDDM. Furthermore there is an even greater incidence of morbidity and mortality from the complications of macrovascular disease, i.e. peripheral vascular, cerebrovascular, and coronary heart disease (34,35). Although more detailed discussions on the prevention of these complications are addressed elsewhere in this symposium there is good evidence from animal models and retrospective studies in diabetic subjects that chronic hyperglycemia is associated with the microvascular and neuropathic complications (36,37).

From epidemiological studies linking specific glucose concentrations with microvascular disease the Canadian Diabetes Association has recommended a lowering of blood glucose in patients with NIDDM to less than 140 mg/dl fasting, and less than less than 200 mg/dl postprandial (38). At this time it is far less clear which factor is most important in the genesis of the macrovascular disease. Many of these subjects have hyperlipidemia even in the presence of well-controlled blood glucose concentrations (39), eighty percent are obese (40), and a significant number have associated hypertension (41). These are documented risk factors for accelerated large vessel disease. With regards to the diabetes it has been documented that patients with newly diagnosed noninsulin-dependent diabetes already have an increased prevalence of coronary artery disease documented by history and/or electrocardiographic evidence of myocardial infarction and angina (42,43). It has also been documented that patients with impaired glucose tolerance are at increased risk for macrovascular complications (44). Whether mild elevation of blood glucose is an etiologic factor or merely a marker of risk is not known (44).

Thus it remains uncertain whether the recommendation for glucose control in NIDDM should be to achieve normoglycemia, e.g. fasting blood glucose less than 115 mg/dl, postprandial less than 140 mg/dl. Similarly elevated basal insulin concentrations have been related to the development of macrovascular disease (46) and animal studies have documented increased lipogenesis and arterial smooth muscle proliferation in the presence of hyperinsulinemia (47,48). These data have led to the hypothesis that the increased insulin concentration often noted in subjects with obesity, impaired glucose tolerance and NIDDM is a significant independent risk factor.

It has often been documented that control of blood glucose with insulin administered by a peripheral route, i.e. the subcutaneous route which is used in the vast majority of patients with IDDM and those with NIDDM on insulin, cannot be achieved without the induction of peripheral hyperinsulinemia (49). This may therefore enhance the risk of large vessel disease. With the above factors in mind our treatment objectives in NIDDM would then be:

(1) to achieve and maintain blood glucose levels at near normal levels, at least 140 mg/dl fasting and 200 mg/dl postprandial; (2) to achieve the first goal while lowering elevated or not raising normal insulin concentrations; (3) to treat other associated risk factors for atherosclerotic disease which include elevated lipid levels, hypertension and smoking.

How can the physician achieve these goals and where do the oral hypoglycemic agents fit into the scheme?

There are four prescriptions which are used in the treatment of NIDDM. These are diet, exercise, oral hypoglycemic drugs and insulin. It is clear from many studies and as discussed in detail in the previous paper that diet is the cornerstone of therapy for NIDDM. Firstly since 80% of patients are obese (greater than 120% ideal body weight) it is desirable for many reasons to have these subjects decrease their weight. Weight loss will usually achieve all three goals at once. Thus blood glucose concentrations will fall at the same time as plasma insulin levels decrease (50). From the preceding discussion this is the ideal situation. Furthermore by more specific alterations in carbohydrate, polyunsaturated and saturated fat ratios, improvement in lipid concentrations, i.e. decreased triglycerides and low density lipoprotein cholesterol levels, will often be attained. Thus there is clearly no substitute for diet. Exercise has often been cited as an adjunct to therapy (51). However the amount and type of exercise and its benefit with regard to the three goals remains to be defined. In controlled studies despite a significant improvement in insulin sensitivity little alteration in glucose concentration has been achieved (52). As well relatively prolonged and intense exercise is required to raise high density lipoprotein concentrations (53). It would seem reasonable however to prescribe some exercise for patients with NIDDM keeping in mind the large number of newly diagnosed subjects who already have symptomatic or asymptomatic large vessel disease.

When diet fails, defined as blood glucose concentrations remaining above target levels one is left with the option of using oral hypoglycemic agents, i.e. sulfonylureas, metformin or both, or insulin. The failure of diet therapy is common. The reasons for this are complex and range from lack of enthusiasm of the physician or patient to hypotheses regarding abnormal regulation of the hypothalamic satiety center mediated by dietary, gut or adipose tissue factors (54).

How efficacious are the sulfonylurea drugs? A large number of studies have examined the response to various sulfonylureas in NIDDM (55-62) (Table 1). The responses may be defined as primary failures (those patients who never achieve adequate control of blood glucose despite a maximum dose of sulfonylurea) or as secondary failures (those patients who achieve adequate control of glycemia but at some later time either because of increased dietary indiscretion, an intercurrent illness or presumed progression of the pancreatic insufficiency develop recurrence of hyperglycemia). The primary failure rate has varied from

6% to 47%. The reasons for this wide range include variable criteria for attempting a trial of sulfonylurea drug therapy. In general it has been observed that overweight patients respond better presumably because their degree of insulin deficiency is less severe. As well subjects with diabetes of less than five years duration have a better response to therapy (5). Thus variation in the numbers of such subjects in different studies will affect outcome. Thirdly in some studies the attempts at primary dietary management were more aggressive. In this way fewer patients with milder disease manageable by diet were included in the sulfonylurea group (62). Thus there exist a large number of patients who respond well to oral hypoglycemic agents who would also respond well to diet. The usefulness of oral medications for such patients will not diminish until the secrets of achieving a high rate of long term dietary compliance are uncovered. The secondary failure rate is also variable and ranges from 1.5% to 36% per year. In general the longer the follow-up the lower the rate suggesting that most secondary failures occur within the first 1-3 years. Only one study analyzed the "failure" rate of insulin therapy in a parallel randomized fashion. At the end of one year a similar number of patients on insulin (40%) compared with sulfonylureas (32.5%) did not achieve target blood glucose concentrations (62). One likely possibility is that, as seen so frequently, initial dietary compliance (which is important with any adjunctive therapy in NIDDM) deteriorated with time. Although it remains to be proved this likely explains the high rate of early secondary failures.

It is difficult to discuss the sulfonylurea drugs without mention of the conclusions of the University Group Diabetes Program study, i.e. that tolbutamide treatment of NIDDM results in an increased risk of cardiovascular death (63). Whether these results are valid has been the subject of numerous articles and repeated analyses. Three of these were published in 1979. In one review - Kilo, a co-principle investigator does not accept the conclusions of the study and in general recommends the use of these drugs with perhaps the exception of tolbutamide itself, the only drug studied (5). In another, Feinstein, in a detailed methodologic evaluation provides evidence that the clinical trial of placebo versus fixed dose of tolbutamide versus fixed and variable doses of insulin was not designed well to answer the question of cardiovascular events (64). Firstly the patients were not randomized with regard to clinical evidence of cardiovascular disease at entry resulting in significantly more subjects with higher risk in the tolbutamide group. Secondly the blood glucose was not well controlled since fixed doses of medication were used except in the variable insulin group. This is not considered acceptable practice today. Dietary compliance in patients on oral medications was not evaluated. Many patients were switched from one treatment group to another (some more than once) before the end of the trial. Thus many patients included in the tolbutamide group were not taking the drug at the time of analysis or death. Finally postmortem examination was performed to ascertain true cause of death significantly more often in the tolbutamide group. These and other considerations, including five studies which failed to

TABLE 1

CLINICAL EFFICACY OF SULFONYLUREAS

Reference	Drug	Follow-up (yr.)	Primary Failures (%)	- Combined - Total % entire follow-up	Secondary Failures (%/year)
55	Tolbutamide	3	16		36
56	Tolbutamide	5	18		4
57	Tolbutamide	5	-		4
58	Tolbutamide	12	6-21		1.5-2.5
59	Tolbutamide	9	14		2.7
60	Tolbutamide	8	-	79	-
	Chlorpropamide	8	-	69	-
61	Clorpropamide	10	-	70	-
	Glibendamide	10	-		-
62	Chlorpropamide	1	47		23
	Glibendamide	1			42
	Insulin	1			40

confirm the UGDP results (64) have led the American Diabetes Association to publish a policy statment that: "Physicians continue to emphasize dietotherapy as the prime form of treatment for maturity-onset diabetes with appropriate use of an oral sulfonylurea or insulin only after diet therapy alone has clearly failed to achieve desired therapeutic goals. The choice of a sulfonylurea or insulin will be left to the judgement of the physician after discussion with the patient" (65).

A negative opinion of the latest UGDP report is that no evidence of a positive effect on mortality by treatment with oral agents or in fact insulin was evident, the implication being that even a remote likelihood of a harmful effect should discourage the use of any hypoglycemic drug (66). However it has recently been demonstrated that prolonged control of blood glucose with an oral hypoglycemic agent, glipizide, results in a decrease in capillary basement membrane thickness (67). At the same time the less well-controlled untreated group had an increase. These data suggest that control of blood glucose by any therapeutic manoeuvre is likely to prevent or delay the microvascular complications. As discussed above the influence on macrovascular disease must remain speculative. If hyperinsulinemia is truly an important pathogenetic factor, enhancement of insulin action may not be beneficial. On the other hand since oral agents do not increase insulin levels with chronic use, they may be a better form of treatment than exogenous insulin administration.

Much of the discussion of the sulfonylureas is also applicable to metformin. It should be noted that apart from the Canadian monitoring study for lactic acidosis few long term studies have been performed with metformin (19,68,69). Clearly the drug is safe if prescribed as indicated. It also has the theoretical advantage of lowering blood glucose without altering insulin concentrations. The blood glucose lowering potency of metformin both in the short term and longer term appears to be somewhat less than the sulfonylureas (19,31,68-70). In the studies discussed above using sulfonylureas the mean decreases of fasting blood glucose concentrations were variable and ranged from 60 - 150 mg/dl. In contrast this range has been 40 - 70 mg/dl for metformin except for one study where diet and drug therapy were introduced simultaneously (31,68-70). The implication of these results is that if the goal of a fasting plasma glucose (equal to or less than 140 mg/dl) is to be reached with metformin therapy the patient should not have an initial fasting plasma glucose higher than the 200-220 mg/dl range. If the latter concentration is achieved by diet therapy or with prior addition of sulfonylurea drugs metformin may be added with a good chance of success. On the other hand biguanide treatment of a patient with a fasting glucose of 300 mg/dl is clearly inappropriate. A similar line of reasoning is not possible with the use of sulfonylureas. Although the latter drugs are more potent glucose lowering agents it has not been possible to predict outcome based on initial blood glucose. The reason may be that the action is primarily dependent on B-cell stimulation. Thus a combination of residual B-cell mass and degree of insulin resistance may determine the response. At the present time there are no easy reliable methods to determine the residual B-cell mass or function (71). This lack of knowledge in the clinic setting results in the prevalent practice of "trials" of oral hypoglycemic agents usually for one to three months before a decision regarding success or failure is reached. This is clearly an area where further investigation would be helpful.

Another effect of metformin that has been viewed as beneficial in the overweight noninsulin-dependent diabetic is the tendency for patients on this drug to lose or at least not gain weight (19,62). Whether this effect is due to decreased glucose absorption or the induction of mild anorexia due to gastrointestinal side effects is still not clear (24). Nevertheless after a one year follow-up of patients randomized to insulin, sulfonylurea or metformin treatment, those on insulin and sulfonylurea had a significant weight gain while those on metformin did not change (62).

Since a major goal of therapy is to prevent macrovascular disease and serum lipid abnormalities are common in subjects with NIDDM, it would be an added benefit if any therapeutic agent would improve lipid levels. Most studies suggest that apart from the lipid lowering effects associated with improved glycemic control there are no such beneficial effects of sulfonylureas (72). Metformin, on the other hand, may improve lipid levels but only in a small number of patients (24,72). This drug is not widely used as a lipid lowering agent.

Special recommendations for the use of oral hypoglycemic agents

What then is the "ideal", or better expressed "acceptable", situation based on the above considerations, goals of therapy and current knowledge? We may conclude that control of glycemia at least to levels where the risks of development of microvascular disease and neuropathy are limited is clearly indicated. Whether even stricter control of glucose concentration will reduce the incidence of macrovascular disease is not known. In order to achieve this goal it is agreed that diet therapy is the modality of first choice.

The duration of this "trial" of diet is not agreed on primarily because physicians feel that they may improve compliance at a follow-up visit by threats, pleading, bargaining, psychotherapy or showing laboratory result to the patient. This delay should not be prolonged lest the symptoms of hyperglycemia continue unabated or the known risks of long-term hyperglycemia are increased. In general one to three months should be more than adequate. With diet failure either sulfonylurea or metformin (if fasting blood glucose equal to or less than 220 mg/dl) may be added to the regimen provided no contraindications exist. Once again there is no general agreement on the length of trials of oral hypoglycemic agents but six to eight weeks is adequate time to reach a conclusion. If at this time adequate control of glycemia is still not attained at maximal therapeutic or tolerated doses one may add an agent from the other group of oral medications. A common sequence of events is the attainment after diet and sulfonylurea therapy of a fasting blood glucose of 200 mg/dl. At this point metformin may be added. The choice of sulfonylurea is a personal matter and depends on the other effects of these agents such as promotion of water retention or water excretion (73). There do not appear to be major differences with regard to glucose lowering potency (74,75). (One should not confuse potency on a weight basis between first and second generation agents with clinical potency at maximal doses). Some physicians prefer to avoid tolbutamide because it was the only agent studied and incriminated by the UGDP and because compliance is decreased by the necessity for multiple daily administration.

Another approach advocated by a minority of diabetologists is to proceed directly to insulin therapy if diet fails. This view stems partly from the results of the UGDP study, partly from the lack of evidence suggesting any advantage of oral agents over insulin in achieving the treatment goals, and partly from the fact that a significant number of patients will require insulin eventually in any case (secondary failures). The benefit of an oral medication over daily subcutaneous injections to lifestyle and the decreased risk of severe hypoglycemia are factors which should also be considered. The theoretical disadvantage of prolonged hyperinsulinemia which may be avoided by oral agents on the development of macrovascular disease requires further investigation.

Another modality of treatment which is under active investigation in a number of centers in the U.S. is the combination of an oral hypoglycemic agent with insulin (76,77). The theoretical benefits of improving insulin sensitivity in these subjects while also administering insulin are attractive. At this point only small effects in short term studies have been documented (76). It remains unclear whether combination therapy will develop into an important alternative.

Situation in Canada

Since the use of oral hypoglycemic agents has been controversial in the medical literature it is not surprising that great variability exists in their use across the country. As of 1983 diabetes mellitus was diagnosed in approximately 1.25 million Canadians (78). This number is estimated to increase by 6% per annum. Eighty percent of these are type 2 or noninsulin-dependent diabetics and may at some point in the course of their disease be considered candidates for oral hypoglycemic agents. All the oral hypoglycemic agents available in Canada are listed in Table 2. During physician visits for diabetes mellitus insulin was mentioned as a drug 58% of the time and oral hypoglycemics 42% (78). Assuming that at least 20% of patients treated have IDDM and are on insulin and these are subtracted from the insulin group the number of patients with NIDDM (80% of total) treated with insulin and oral hypoglycemic agents are approximately equal, i.e. 38% and 42% respectively.

(This ratio may be somewhat higher for the oral agents since some patients with NIDDM would be on diet alone and not included in a drug mention group). It is clear that oral hypoglycemic agents are widely used in Canada. It is estimated that with a population of increasing age the worldwide market for these agents is expanding by 30% per year. Another point of interest is the variation across Canada in the use of the sulfonylureas and biguanide. The greatest use of metformin is in Quebec perhaps reflecting the European influence where this drug is popular (20). On the other hand the influence from the U.S. would be to use the sulfonylurea drugs since metformin is not approved for use in that country.

The real question of appropriateness of use of these drugs can only be assessed by examining individual physicians' approaches to the treatment of NIDDM. This information is not available at this time. Therefore, I have conducted a limited survey of family practitioners across Canada (the majority of patients with diabetes mellitus are attended by a general practitioner, 69% (78)) using a short questionnaire. The response was incomplete as of this date and therefore only certain centers are represented.

The questionnaire addressed the following issues in NIDDM:

1. Whether initial treatment should be diet alone, or diet combined with drug therapy.

2. Length of time of "trial" of diet.

3. Attitude towards the use of sulfonylureas.

4. Attitude towards the use of metformin.

5. Whether the physician felt that insulin was a better agent than oral hypoglycemic agents, provided the same degree of glycemic control is achieved.

6. Experience with combinations of different sulfonylureas.

7. Experience with the use of combinations of oral hypoglycemic agents and insulin.

The results are shown in Table 3, 4 and 5.

It is seen that almost all physicians understand the importance of diet therapy as the initial and most important therapeutic manoeuvre in NIDDM. Some physicians persisted in encouraging dietary compliance for prolonged periods of time despite elevated blood glucose concentrations (Table 3). The first drug chosen as an adjunct to diet therapy was a sulfonylurea in the majority of cases (Table 4) This was despite a plasma concentration which may have been lowered as effectively by

TABLE 2
ORAL HYPOGLYCEMIC AGENTS AVAILABLE IN CANADA*

PRODUCT MANUFACTURER YEAR OF INTRODUCTION	TABLET STRENGTH	ESTIMATED DURATION OF ACTION	ESTIMATED DAILY DOSAGE
DIMELOR		12-24 hrs	250mg-1.5g
Acetohexamide	500mg		
(Lilly) 1963			
DIABENESE		24 hrs	100-250mg
Chlorpropamide	250mg		
(Pfizer) 1958	100mg		
CHLORONASE		24 hrs	100-250mg
Chlorpropamide	250mg		
(Hoechst) 1967	100mg		
NOVOPROPAMIDE		24 hrs	100-250mg
Chlorpropamide	250mg		
(Novopharm) 1969			
APO-CHLORPROPAMIDE		24 hrs	100-250mg
(Apotex) 1974	250mg		
	100mg		
CHLORPROPAMIDE		24 hrs	100-250mg
(D.T.C.) 1977	250mg		
STABINOL		24 hrs	100-250mg
Chlorpropamide	250mg		
(Horner) 1967			
EUGLUCON		24 hrs	5-10mg
Glyburide	5mg		
(USV) 1977	2.5mg		
DIABETA		24 hrs	5-10mg
Glyburide	5mg		
(Hoechst) 1971	2.5mg		
GLUCOPHAGE		24 hrs	1.5g
Metformin	500mg		
(Nordic) 1975			
ORINASE		6-12 hrs	.5-1g
Tolbutamide	500mg		
(Hoechst) 1957	1g		
TOLBUTAMIDE		6-12 hrs	.5-2g
(Sands) 1972	500mg		
MOBENOL		6-12 hrs	.5-2g
Tolbutamide	500mg		
(Horner) 1957			
NOVOBUTAMIDE		6-12 hrs	.5-2g
Tolbutamide	500mg		
(Novopharm) 1968			
APO-TOLBUTAMIDE			
Tolbutamide	500mg	6-12 hrs	.5-2g
(Apotex) 1975			
TOLBUTAMIDE		6-12 hrs	.5-2g
(D.T.C.) 1971	500mg		

* Courtesy IMS Canada 1983 (78)

metformin. The reasons for this are evident in the answers to the questions regarding physicians' habits in prescribing these medications. About half of the physicians always or often use sulfonylureas in the treatment of NIDDM. However very few always or often use metformin (the majority - rarely or never) (Table 3). The reasons cited by those not using sulfonylurea include most commonly that "the drugs discourage the patients from following their diets and prevent weight loss" (Table 5). Some physicians believe that they are not effective therapy, and several that they cause an increased incidence of cardiovascular complications. It should be noted that only one was not familiar with the sulfonylureas. In contrast the major reason cited for not using metformin was lack of familiarity with the drug (Table 5). The reasons for this are unknown but may be a result of the influence of a large amount of U.S. advertising of sulfonylureas with none of metformin. A significant number of physicians also are not aware of the drug monitoring of metformin (23) and equate the danger of lactic acidosis induced by phenformin to all biguanides. Only three believed it was not effective therapy and one of these had also admitted not being familiar with the drug.

Ten of forty-six physicians across Canada believed that insulin therapy was better than that with oral hypoglycemic agents provided the same degree of glycemic control is achieved. Other than the UGDP study which has been discussed in detail there is no evidence to suggest this (Table 3).

Seven physicians of 46 had combined more than one sulfonylurea as treatment and found it to be more successful than maximum doses of a single agent (Table 3). There is little evidence to suggest that this should ever occur (74). One possibility which may explain this finding is that maximal doses of one agent were not achieved. As metabolism of sulfonylureas among subjects is variable (79) and blood concentrations are not available to the clinician, there may be a few instances when this occurs. However it is also possible that a few physicians are using these medications incorrectly. Finally, although an area of current interest, there was evidence that insulin was being combined with oral hypoglycemic agents in only one center (Halifax) (Table 3). It is not clear whether this was done in the course of a controlled clinical trial. There is evidence from the U.S. that a number of physicians are using this type of therapy without waiting for results of controlled investigations (80). At the present time such combination therapy should be considered experimental.

Conclusions and Recommendations

The overall impressions from this limited survey are that the opinions and practice of physicians across Canada reflect to a great degree that of the medical literature, the majority opting for diet therapy followed by oral hypoglycemic agents if necessary. A small number are still reluctant to use them because of the UGDP results. A large number are not aware of the possibility of use of metformin,

TABLE 3

PRACTICE AND ATTITUDES OF GENERAL PRACTITIONERS IN CANADA TO TREATMENT OF NIDDM.

CITY		MONTREAL	CALGARY	HALIFAX	WINNIPEG	TOTAL
Number of responders*		18	15	9	4	46
1. Initial Treatment	Diet alone	15	15	9	4	43
	Other	3	0	0	0	3
2. Duration of Trial of Diet Therapy	3 Mo.	10	9	7	0	26
	6 Mo.	6	3	1	2	12
	6 Mo.and over	2	3	1	2	8
3. Use of Sulfonylureas**	+	11	10	9	0	30
	-	7	5	0	4	16
	N.R. †	0	0	0	0	0
4. Use of Metformin**	+	0	2	4	0	6
	-	17	13	5	4	39
	N.R.	1	0	0	0	1
5. Insulin better than O.H.A. ††	Y	4	3	1	2	10
	N	14	11	8	2	35
	N.R.	0	1	0	0	1
6. Combined Sylfonylureas	Y	2	1	2	2	7
	N	16	14	6	2	38
	N.R.	0	0	1	0	1
7. Combined Insulin With O.H.A.	Y	0	0	3	0	3
	N	18	15	5	4	42
	N.R.	0	0	1	0	1

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* Twenty questionnaires were sent to each city

** + denotes the answer "always" or "often"; - denotes "rarely" or "never"

† N.R. = No response. The question was not answered

†† O.H.A. = oral hypoglycemic agent

TABLE 4

THE FIRST HYPOGLYCEMIC DRUG CHOSEN AS AN ADJUNCT TO DIET THERAPY IN NIDDM BY CANADIAN GENERAL PRACTITIONERS

CITY	MONTREAL	CALGARY	HALIFAX	WINNIPEG
Number*	16	12	8	2
DRUG				
Sulfonylurea	15	9	7	2
Metformin	0	1	1	0
Insulin	0	2	0	0
**Consultation	1	0	0	0

* Number of physicians opting for drug therapy after 3 or 6 months of diet failure. The remainder chose to continue diet alone (see Table 3).

** One physician chose to consult a specialist for management of diet failure.

TABLE 5

REASONS CHOSEN IN ORDER OF FREQUENCY FOR "RARELY" OR "NEVER" USING ORAL HYPOGLYCEMIC AGENTS BY CANADIAN GENERAL PRACTITIONERS

CITY*	M	C	H	W	TOTAL
A. SULFONYLUREAS					
1. They discourage the patient from following their diets and prevent weight loss	6	3	0	2	11
2. They are not effective therapy	1	2	0	3	6
3. They cause an increased incidence of cardiovascular complications	2	2	0	0	4
4. I am not familiar enough with these drugs to use them regularly	0	1	0	0	1
5. They have too many adverse side effects other than above	0	0	0	1	1
B. METFORMIN					
1. I am not familiar enough with this drug to use it regularly	8	10	2	3	23
2. It causes a significant incidence of lactic acidosis	7	2	3	2	14
3. It is not effective therapy	1	2	0	0	3
4. It causes an increased incidence of cardiovascular complications	2	0	0	0	2
5. It has too many adverse side effects other than above	1	0	0	0	1

* M = Montreal, C = Calgary, H = Halifax, W = Winnipeg

presumably a result of lack of advertising and little mention in our predominantly U.S. sources of medical literature. It is clear that some re-education of physicians and guidance are required with regard to (1) length of time for a trial of diet therapy, so that blood glucose concentrations are not ignored for prolonged periods, (2) appropriate use of sulfonylureas, and (3) availability and appropriate use of metformin. As well a larger and more representative survey of physicians across Canada is needed.

We may also state that many of the questions regarding the use of oral hypoglycemic agents cannot be answered because our knowledge is limited.

(1) Should we aim for normoglycemia in NIDDM presuming that even minor elevations of glucose play a role in macrovascular disease?

(2) Might therapy with oral agents be preferable to insulin in NIDDM because of the role of hyperinsulinemia in the pathogenesis of macrovascular disease?

(3) Is there a role for combined therapy with insulin and oral agents in NIDDM?

(4) Is there a role for oral agents in the treatment of impaired glucose tolerance to prevent either the development of macrovascular disease or overt diabetes mellitus? (81, 82)

(5) What are the biochemical mechanisms of action of these oral agents? Knowing these mechanisms and the pathogenetic abnormalities in NIDDM, might there be a way of predicting with more certainty which patients will respond to these agents?

The answer to these questions would obviously be desirable so as to settle controversy and make treatment of NIDDM more successful and therefore more "ideal". Additional significant basic and clinical research support in these areas is the only means by which these answers will be obtained.

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FORMULATIONS AND APPLICATIONS OF INSULIN IN THE MANAGEMENT OF DIABETES MELLITUS

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The overall objectives in management of diabetes mellitus include the restoration and maintenance of optimum health, prevention or postponement and early detection of the long-term complications of the disease, and the ability to deal with specific situations, e.g. pregnancy, surgery and concurrent illness (1). In the context of various components of the therapeutic armamentarium available to health care professionals, insulin is by far the most important pharmaceutical, and is complemented by advice with respect to nutrition (principally adjustments to intake of carbohydrate, protein and calories,) to appropriate forms of exercise and their relationship to meals, to methods of self-monitoring, and to appropriate interactions with health care professionals.

A. Impact of Various Aspects of Diabetes upon Applications of Insulin

1. Types of Diabetes Mellitus

In general about 15% of diabetes mellitus is type 1 (insulin-dependent, IDDM); 70% is type 2 (non-insulin-dependent, NIDDM), the great majority being overweight, with an intermediate group of the remaining 15% somewhat more difficult to classify (2,3). Type 1 diabetes is characterized by youthful onset (before the age of 30), thinness, symptoms suggestive of hyperglycemia and ketosis. Except during the "honeymoon" phase, insulin therapy is essential for survival.

Features of type 2 diabetes include later onset, fatness, metabolic stability and resistance to ketosis. Indications for insulin therapy in type 2 diabetes include symptoms of hyperglycemia and long-term complications which, in the opinion of the physician concerned might be ameliorated. Overall, about 30% of those with recognized diabetes (or about 1% of the general population) are committed to long-term insulin therapy, and additional patients require insulin during pregnancy or concurrent illness.

Conventional treatment in type I diabetes includes insulin therapy based on multiple daily injections and use of mixtures of short-acting and intermediate/long-acting insulins.

Insulin therapy in type 2 diabetes is more likely to be based on a single injection or a single pharmaceutical. Use of insulin in type 2 diabetes reflects the judgment of physicians as to indications relative to the safety or efficacy of the alternative. The conclusion reached by the University Group Diabetes Program (UGDP) study with respect to the hazard of tolbutamide (a sulphonylurea) (4) is responsible for the apparent increased utilization of insulin in type 2 diabetes in the

U.S.A. Many patients with type 2 diabetes and some patients with type 1 diabetes maintain significant beta cell function over long periods of time, conferring a degree of metabolic stability not present in the absence of endogenous insulin secretion (3,5,6).

2. Achievement of Objectives of Therapy

In states of acute decompensation (diabetic ketoacidosis or hyperosmolar coma), the goal of therapy is the short-term reversal of metabolic, acid-base and circulatory abnormalities, and a reversion to an asymptomatic state. In current practice, undiluted regular insulin is given by intramuscular or subcutaneous injection or is infused in conjunction with intravenous fluids (solution prepared by a nurse or hospital pharmacist) with careful dosage monitoring under the supervision of a physician (7). Although significant adsorption of insulin occurs into the plastic used in intravenous bags and lines (8), current practice suggests that additives (albumin for example as an insulin-transporting agent) are not necessary (9).

Short-term requirements for insulin to meet changing needs and treatment goals during pregnancy or surgery in normally non-insulin-requiring patients frequently are identified. As the original reports suggested that intermittent insulin therapy was a risk factor for the emergence of insulin resistance (by definition in adults, a need for more than 200 U/day for 2 days) (10), where temporary insulin therapy is anticipated, insulin of minimal immunogenicity should be used.

During the long-term treatment of insulin-requiring patients with diabetes mellitus, the glycemic goals of therapy are determined in large part by the clinical features of the case, patients' and physicians' perceptions of current practice and scientific evidence. Conventional therapy in type 1 diabetes includes one or two injections daily of at least an intermediate or long-acting insulin (NPH/Lente or Protamine Zinc/Ultralente); or more commonly (particularly in academic centres), mixtures of short-acting (Regular, Semilente) and intermediate or long-acting insulins. More complex programs may be applied depending upon the ability or inability on the part of the patient to achieve the glycemic goals perceived to be optimal in the particular case. These forms of so-called "intensive insulin therapy" include: (1) 3 or 4 injections per day of short - and intermediate/long-acting insulin; (2) delivery via an indwelling needle or cannula (continuous subcutaneous insulin infusion, CSII. or insulin "lock"; or (3) jet insulin injection, using a spring-loaded device (e.g. Medijector) (11).

The unphysiological nature of the subcutaneous route of delivery is an obvious reason for a number of the problems related to the application of insulin. The inter- and intra-patient variability of pharmacokinetics has been studied extensively (12). Despite the problems of absorption, patients are taught, and indeed appear to make adjustments in dosage to regular and/or intermediate insulin effectively, depending on results of home blood glucose monitoring, anticipated levels of activity, and carbohydrate intake. Although alternative routes of administration are under review (intravenous (13), intraperitoneal (14), nasal (15) and others), a number of strategies have been investigated in attempts to improve the efficacy of subcutaneous insulin. For example,replication of the rapid rate of rise of serum insulin (a recognized physiological phenomenon thought to be important in control of post-meal glycemia) has been studied in terms of the ratio of short- to intermediate -acting insulins. Most programs incorporate some form of intermediate or long-acting insulin to provide the analogue of the basal insulin secretory rate required for overnight glycemic control. In ratios of more than one part regular to two parts NPH or Lente insulin used, adequate "bioavailability"* of regular insulin is demonstrable in normal volunteer subjects (lacking anti-insulin antibodies) (16). In addition to the types and proportions of insulin in mixtures, efficacy is subject to variation according to a large number of factors including the interval between the injection and the ingestion of food, and the site and other factors related to the injection (12,18).

In terms of achievement of the objective of preventing complications, there is as yet no indisputable evidence that therapeutically attained glycemia by any available means will prevent or postpone microvascular complications (19). At the present time therefore, the cost and benefits of all components of treatment of the insulin requiring diabetic should be assessed in this context. Although there have been suggestions that insulin:antibody complexes may exert a pathophysiological role in the vasculopathy (20) of diabetes, there is little actual evidence for this (21). The concept is therefore not an acceptable rationale for generalized prescription of high-cost preparations with low immunogenicity.

The relationship of forms of insulin therapy to the well recognized tendency of patients with diabetes mellitus to develop macrovascular disease is unclear. Although the measurement of circulating free insulin in the serum of insulin-treated patients with diabetes is imperfect, our data (albeit obtained for the most part in patients having anti-insulin antibodies) suggests that supranormal levels of free insulin are associated with both conventional and intensive forms of insulin therapy (22). Hyperinsulinemia is considered to promote lipogenesis and in fact atherosclerosis, but the relationship of atherosclerosis to glycemic control is unclear, and any judgement as to the relevance of hyperinsulinemia to macrovascular disease during insulin therapy would be premature (23).

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* "Bioavailability is defined as the percentage of a drug contained in a drug product that enters the systemic circulation in an unchanged form after administration of the product. The concept also includes the rate at which this entry occurs." (17).

In many patients, "near-normoglycemia" can be attained with current methods of blood glucose monitoring and insulin delivery. Although the frequency of severe hypoglycemia does not appear to be increased under conditions of controlled trials of intensive therapy, current clinical concern suggests that efforts be made to minimize the frequency and optimize the treatment of such episodes. The contribution of hyperinsulinemia, and in particular antibody bound insulin to the prolongation of hypoglycemia in insulin-treated patients with diabetes has been recently discussed (24). The continuing availability of glucagon suitably prepared for patient use is to be encouraged.

With respect to the goals of therapy in pregnancy which include a healthy fetus, normoglycemic at birth, there is some evidence that in addition to the attainment of maternal normoglycemia, fetal islet hyperplasia may be decreased in the absence of circulating anti-insulin antibodies of maternal origin (25), justifying the use during pregnancy of formulations with minimum antigenicity.

B. Future Trends and Special Formulations

There are at least 15 insulin manufacturers in the western world, resulting in a competitive marketplace conducive to pharmaceutical and clinical research. The obsolescence of protamine zinc insulin is becoming apparent, presumably due to relatively unpredictable effects in comparison to Ultralente insulin derived from beef and, more recently, semi-synthetic human Ultralente insulin (26). Human biosynthetic proinsulin has been investigated as an adjunct to "native" insulin with prolonged duration and with possibly a selective effect on hepatic glucose output (27). Highly concentrated (U-500) porcine insulin (PI) has been applied in cases of insulin resistance (28) and in an experimental program of use of nasal insulin (15). Advances in the biosynthesis of human insulin using recombinant DNA encoded for proinsulin are being reported (20). Delivery of insulin from an implantable biodegradable polymer container capable of variable insulin release has been investigated in animals (30). The oral administration of insulin incorporated into liposomes has been reported to be effective in diabetic rats (31). The continuing prospects of improved methods of continuous (pump) insulin infusion necessitating the prolonged storage of insulin in pumps at body temperature has stimulated a search for preparations with required characteristics. Sulfated insulin has in particular been examined in this regard (32,33). The microencapsulation and implantation of surviving Islets of Langerhans provide an artificial beta cell of a biological nature with potential application in the future (34).

Improved methods of the study of pharmacokinetics of insulin will undoubtedly stimulate further advances in formulations and modifications to existing formulations which will improve bioavailability and safety (35).

C. Relevant Aspects of the Secretion, Transport and Action of Insulin

The insulin secreted contains 51 aminoacids arranged into A and B chains attached by two sulfhydryl bonds, and assumes a tertiary structure. A precursor, proinsulin, is enzymatically cleaved intracellularly as part of the biosynthetic process, resulting in storage granules containing insulin and a connecting-peptide (C-peptide) which are released into the pancreatic vein in equimolar amounts. A continuous secretion of insulin normally occurs, punctuated by periods of increased secretion and subject to neural, hormonal and biochemical stimuli. The insulin polypeptide circulates in a free state normally but, in the presence of anti-insulin antibodies, a portion of secreted insulin may be bound to these antibodies ("insulin-transporting globulin") (36). Likely biologic action of insulin may be modified by antibody binding, the availability of insulin being conditional upon the degree of affinity of the antibodies for the polypeptide (12, 37). For example, high affinity antibodies might compete strongly for insulin, denying access to insulin receptors which are present in many tissues. The important biologic actions of insulin appear to be with respect to liver, muscle and adipose tissue where insulin receptor binding promotes the transport of glucose and other substrates, and appears to activate intracellular processes (kinases) which in turn modulate the activities of critical enzymes in metabolic pathways, often by a process of phosphorylation or dephosphorylation (38).

D. Classification of Characteristics of Pharmaceutical Preparations, with Comments on Significance

1. Species of Origin

The traditional sources of insulin are beef cattle (1922) (bovine, BI) and pigs (1923) (porcine, PI). For reasons of availability of supply, insulin has been prepared in a proportion of 70-90% bovine and 10-30% porcine in beef-pork (BP) combinations. Pancreata of single species provided by slaughter houses dealing with both species cannot be assumed to be uncontaminated with other species of origin. The molecular structure and aminoacid composition of these and a number of other insulins including human pancreatic insulin (pHI) are known. Although BI and to a lesser extent, PI differ slightly from pHI in terms of aminoacid composition, studies of receptor interaction indicate that these three insulins are similar at the biologically active site on the polypeptides (39). In addition, studies with biosynthetic human insulin (bHI) suggest that interaction with anti-insulin antibodies and islet cell receptors for insulin are identical. Thus, any suggestions of difference in the pharmacokinetic properties of BI, PI, or bHI are most likely to be related to the properties of the pharmaceutical preparation interacting with characteristics of the recipient.

Through the 1970's, concern that the antigenic properties of existing insulin preparations might be contributing adversely to management and outcome in diabetes therapy was paralleled by increasing expertise in the purification of polypeptides. This stimulated the appearance of animal insulins of increasing purity, initially in Scandinavia, and with the application of recombinant DNA technology, which was potentially applicable industrially, to the production of human insulin. Thus by 1980 the Eli Lilly Company was in a position to test biosynthetic human insulin (bHI) produced by two separate clones of E coli programmed to produce the A or the B chains (which were combined biochemically) and highly purified to eliminate non-insulin chain combinations and bacterial byproducts (40). Likewise, Danish pharmacologists developed semisynthetic human insulin (sHI) with a chemical modification (transpeptidation) of highly purified PI (41).

2. Formulations of Insulin

The classification of insulins according to time of onset and duration of action has been standard for many years (38). The original fast-acting preparations have evolved into insulin made from zinc-insulin crystals (regular insulin), which has an approximate time of onset of one hour with a duration of action of 6-8 hours (38) and prompt insulin-zinc suspension, USP (Semilente or amorphous) insulin which has a somewhat longer duration of effect (14 hours).

The intermediate-acting insulins, NPH (isophane insulin suspension, USP) and Lente (insulin-zinc suspension, USP) show approximate onset of action at two hours, and duration of action of 24 hours, while the long-acting insulins, protamine zinc suspension, USP (PZI) and Ultralente (extended insulin zinc suspension, USP) show approximate time of onset of action of 7 hours, with durations of effect of 36 hours. These specifications are however subject to prolongation in the presence of IgG insulin antibodies (12) and to both inter- and intra-patient variation. In addition, some reports suggest a more rapid onset and shorter duration of action of regular and NPH preparations of bHI (42), but extensive studies of the kinetics of bHI in comparison to PI do not confirm this (43).

The relative advantages and disadvantages of NPH and Lente insulins are of potential importance (44). The bioavailability of regular insulin mixed with NPH appears to be diminished beyond ratios of 1:2. Bioavailability of regular insulin mixed with Lente insulin appears to be if anything less, particularly if mixed with Ultralente insulin (12) or if left to stand prior to administration (45). However Lente (a mixture of 70% Ultralente insulin, crystallized with zinc from an acetate buffer and 30% Semilente (amorphous) insulin, also derived in the presence of zinc from an acetate buffer) may be adjusted in terms of its maximal time of effect and duration of action by variation in the proportion of Semilente to Ultralente insulins in the preparation.

Mixtures of insulins with different times of action permit some degree of individualization on the part of the physician or the patient. Mixtures may be prepared by the patient at the time of injection, by the pharmacist using the Lente preparations or by the manufacturer, most recently through the availability of fixed combinations of regular to NPH (1:1, 3:7).

Exposure of BI or PI to sulphuric acid under controlled conditions permits the manufacture of sulfated insulin, a preparation of low antigenicity heretofore important in the management of patients with antibody mediated insulin resistance (46). The time of onset and duration of action is intermediate between regular and NPH insulins. The application of highly purified animal and human insulins of low antigenicity can be expected to render the need for sulfated insulin negligible; however in the Scandinavian countries where highly purified preparations of insulin have been in use for several years, a continuing requirement for SI is apparent. A randomized trial of the efficacy of sulfated insulin in comparison with human insulin in insulin-resistant patients will shortly become available. When the results of this trial are available, it is questionable whether the need for SI will continue (47).

3. Purity

In the past decade, the original techniques of insulin extraction have been extended to include gel filtration and ion exchange chromatography, resulting in preparations which have been known as "monocomponent" insulins. This processing is associated with a significant (though difficult to quantify) loss of the original pancreatic insulin content, but has largely eliminated contamination with components containing proinsulin, degraded insulin (desamido- and arginyl-insulin) and other hormones of pancreatic origin (glucagon, pancreatic polypeptide, somatostatin, vasoactive intestinal peptide) (48). By convention, preparations containing less than 10 ppm proinsulin are considered "pure" and in fact purified pork insulin now contains less than 1 ppm proinsulin; preparations of bHI are of equivalent purity with respect to contaminating bacterial products and inactive chain combinations.

The advantage of high purity appears to lie mainly in the reduction, but not the elimination of antigenicity, particularly with respect to proinsulin which appears to be a major contaminating antigen.

4. Biophysical State

Within the range of concentration of insulins customarily used (from 40-100 U/ml), little difference in efficacy has been apparent. In use the insulin formulations containing crystals must be gently agitated by the patient to ensure homogeneity of the preparation. The increasing purity achieved with separation procedures during the 1970's made possible the formulation of highly stable insulin at neutral pH which in turn conferred increasing stability during storage and made possible the stability of mixtures of regular insulin and NPH. Permitted shelf life of packaged insulin now is two years, but may be extended to three.

Differences in the nature of the buffer and in the relationship of insulin to protamine vary among manufacturers, and the impact upon mixing and storage of these variables is unclear. Claims with respect to the superiority of buffering systems for particular purposes (e.g. CSII) are plausible but difficult to substantiate.

Preparations vary as to the nature and concentration of preservatives (usually metacresol or phenol) added to inhibit the growth of bacteria within the vial during day-to-day usage. Under conventional insulin injection conditions, the frequency of site abscess formation is rare, although during CSII frequent infections have been reported.

Various manufacturers have developed coding systems based on colour, symbols and tactile stimuli in efforts to minimize the chance of error or confusion on the part of patients selecting their preparations.

E. Implications of Features of Pharmaceutical Preparations

1. Immunogenicity

With increasing purity, significant reductions in contaminants have been achieved and there is little doubt that, in regions where purified insulins have been widely available, rates of immune and allergic phenomena have remarkably decreased, particularly with respect to insulin resistance and lipoatrophy. However, cases of local or systemic allergy (IgG-mediated) continue to occur (49), and the demand for sulfated insulin in Scandinavia for use in cases of insulin resistance or allergy remains.

In explanation for the continuing evidence of these immune phenomena, it must be remembered that: (1) anti-insulin antibodies are detected in type 1 diabetes prior to insulin administration (50); (2) in the presence of high quantities of zinc, polymers of even highly purified human insulin may occur and be antigenic; (3) the primary structure of beef and of pork insulin are in fact slightly different to that of human insulin; and (4) protamine and zinc themselves may be allergenic in some cases (44); and (5) it is unlikely that the entire injectate is completely soluble in extracellular fluid (48).

With respect to the relative immunogenicity of available insulin preparations, it is generally acknowledged that BI, even when highly purified, is somewhat more antigenic than HI or PI (51). There is now evidence in a randomized trial in young type 1 patients that, at least in the early stages, significant levels of antibodies are less frequent and of lower titre during treatment with sHI than with purified pork insulin (52). Similar data has been presented in an unrandomized fashion for bHI (53). Evidence for a predeliction to production of anti-insulin antibodies on the part of patients with type 1 diabetes having the HLA haplotype DR 4 has been presented (54).

The significance of these immune phenomena is under debate. In children, the C-peptide activity indicative of persisting beta cell function was diminished in the presence of insulin antibodies (55) but in adults, contrary evidence was found (56). The transplacental passage of anti-insulin antibodies may impair fetal beta cell function (25).

2. Bioavailability

All preparations share the same basic problem of access to the general circulation inherent in the use of the subcutaneous insulin injection site. There appears to be no primary relationship in terms of the kinetics of insulin pharmaceuticals to the species of origin other than the suggestion that anti-insulin antibodies may compete for free insulin being released from the injection site and "blunt" the expected insulinemic response (36). The bioavailability of regular insulin may be modified according to the proportion of NPH, or in relation to mixture with Lente insulins as discussed above (16).

Studies in normal (presumably no anti-insulin antibodies) and diabetic (with or without prevailing anti-insulin antibodies) subjects have shown no consistent difference in the characteristics of absorption, distribution, clearance, immunoreactive insulin response or disappearance-time with respect to sHI, bHI or purified PI (51). However, as the assignment of potency to various preparations as in the rabbit hypoglycemia or mouse convulsion tests contain up to a 5% error (57), minor differences in pharmacokinetics may be obscured. Furthermore, long-term trials of bHI or sHI have suggested that the duration of action of these preparations may be somewhat shorter than that of PI with equivalent purity (58,59,60). The hydrophilic character of the HI molecule in comparison to PI or BI partially explains the kinetic differences implied (48).

3. Clinical Application

Glycemic control achieved in appropriately randomized trials using readily available preparations of insulin shows no advantage with respect to the species of origin or purity of the insulins used (52,58,59,60,61) and, in some studies, glycemic control tended to be worse during treatment with HI. Interpretation of the latter finding, however, is difficult in the absence of clearly defined goals of therapy. With respect to the predisposition to hypoglycemia attributed to the presence of insulin antibodies in association with hyperinsulinemia (24), there appears to be no evidence in these trials of decreasing rates of hypoglycemia concurrent with decreasing or lower antibody titres.

Current concepts as to the indications for the use of purified pork or human insulins include (62):

(i) insulin allergy or resistance;
(ii) prospective intermittent insulin therapy, (e.g. during surgery);

(iii) pregnancy;
(iv) lipoatrophy
(v) during studies requiring insulin radioimmunoassay to obviate antibodies in competition to the antibodies added as reagent.

4. Economic

An element of the pattern of usage of insulin pharmaceuticals may be due to subjective impressions on the part of medical advisors or diabetic patients as to a desirable pharmaceutical on the basis of the species of origin. This tendency is to be deprecated. Clearly, the pharmaceutical is far different from the insulin molecule as it must exist within the beta cell itself. This concept should be borne in mind in relation to any projected reorganization designed to simplify the prevailing nomenclature.

Impact of the applications of new preparations and formulations of insulins on the long-term health of diabetic populations has yet to be shown. At the present time the actual cost of HI in relation to highly purified (less than 1 ppm proinsulin) PI is unclear. Although the manifest costs are equivalent (in Canada), the real costs may actually be quite different.

F. Current Situation in Canada

1. Specific aspects related to diabetes mellitus in Canada

On the basis of accepted prevalence rates, it is estimated that 160,000 Canadians have Type 1 diabetes and are being treated with insulin. A further 100,000 (approx.) individuals are likely taking insulin for relief of hyperglycemia or other reasons associated with Type 2 diabetes. In the latter group are included subgroups of native Canadians among which the prevalence of diabetes is particularly high (native Canadians). Goals of therapy and acceptable and desirable upper limits of glycemia during therapy have been recommended by the Canadian Diabetes Association (1). The proportion of diabetic individuals treated with insulin and meeting these goals of therapy is unknown, but is likely a minority. There is no reason to expect that morbidity associated with insulin therapy differs from that in other countries whose history of exposure to the evolution of insulin pharmacology is similar (e.g. USA). Deaths related to insulin hypoglycemia have been estimated to occur at a rate of 1/1200-3000 patient years in the UK (63).

2. Provision of health care to insulin-requiring patients in Canada

The specialty and nature of the training of physicians treating diabetic patients in Canada is difficult to determine. It is likely in general that specialists (internists, pediatricians, endocrinologists) are largely involved in the management of patients with Type I diabetes in urban centres, whereas in less populated areas the primary physician is responsible. The continuing medical education of physicians in the use of insulin as a pharmaceutical is provided principally under the auspices of local hospitals, in large part with the support of educational directors of the manufacturers of diabetes care supplies. Education of the patient in techniques of insulin injection is the responsibility in nurses on wards or in outpatient departments or diabetes education centres. Responsibility for supervision of insulin injections in the community lies with public health or Victorian Order of Nurses and this form of supervision is important in the older age group, particularly among those living alone.

3. Insulin related costs in diabetes care in Canada

It is estimated that 2.5 million vials of insulin (2.5 billion units) are used annually with an annual increment of 3 or 4%. The reason for the increment is not clear: an increase in the general population and in the proportion of the population with diabetes, and changing perceptions of the medical profession with respect to insulin needs or therapeutic indications, may be partially responsible.

Manufacturers use a rate of 50 units/patient/day as a basis for market calculations. Using information available in London, Ontario, the wholesale cost for beef-pork preparations ($9) or purified pork/HI preparations ($13.50) are subject to a 10-40% markup at the pharmacy level, giving a possible range of cost of $15-30/mo suggested. Assuming an average cost for insulin of $250 per patient (250,000 patients) indicates an annual retail expenditure for insulin in Canada of approximately $60 million. Insulins used in Canada are mainly regular and NPH. Long-acting insulins (Ultralente, Protamine zinc) are prescribed infrequently.

4. The insulin market in Canada

Currently there are three pharmaceutical firms supplying the Canadian market. Estimates of market share in 1984 were: Connaught and Connaught/Novo, 87%; Lilly, 12%; Nordisk, 1%. Approximately 13% of insulin sold was the more expensive highly purified pork or human types. At the present time, HI and PI have approximately equal share; predictions as to the proportionate and absolute share of the market over the next few years vary widely. Clearly the trend is toward the consumption of more of these insulins, given the indications above and current perceptions on the part of physicians of the available scientific evidence with respect to the immunogenicity of insulins. It might be pointed out that the beef-pork preparations now being marketed are "purified" (less than 10 ppm proinsulin).

Specialized products include the long-standing availability of sulfated insulin, the newly-introduced premixed preparations of regular and NPH insulins, and the soon to be available preparation of semi-synthetic human Ultralente insulin. Protamine zinc insulin (PZI) is no longer being manufactured for the Canadian market, although adequate supplies are said to be available at current rates of consumption. Decisions with respect to withdrawal or introduction of new products to the market appear to be made without reference to the clinical or the scientific diabetes communities.

The significance of the "on shore" need for manufacturing capability (which has been provided historically by Connaught, and now Connaught/Novo) is difficult to assess with respect to prescribing habits of Canadian physicians. Large supplies of imported insulin could be stocked (particularly if the expiry date permitted is extended to 3 years), making a shortage of supply unlikely. However, the impact of fluctuations in the Canadian dollar on the cost of imported insulins is a consideration in terms of stability of cost to the Canadian consumer.

Disposable insulin syringes are in use by an estimated 99% or more of Canadian diabetic patients; an unknown number reuse the supposedly "once-only" disposable syringes for reasons of economy. This practice is not encouraged, but in many cases is tolerated, by health care professionals. The incidence of site infections is low, presumably due to effective bacteriostasis in insulin formulations, but the rate of dosage error due to illegibility of the unit markers on the plastic syringes is unknown.

There are estimated to be 600 insulin pumps in use in Canada, delivering insulin by CSII. Patients are trained and supplied and pumps are maintained through the manufacturers' marketing system. The ethics of the manufacturers in terms of ensuring adequate nursing and medical supervision and education appear to be high. At the present time there are 4 suppliers of insulin infusion pumps in Canada. Use of implanted (intraperitoneal and/or intravenous) infusion devices is rare.

5. Problems of terminology

With the entry into the marketplace of three new manufacturers of insulin there has been an expansion of preparations, often with overlapping and/or identical pharmacological characteristics in the Canadian market. This has led to confusion with respect to terminology and no doubt a major learning and logistic task for wholesale suppliers and pharmacists. I understand that the Health Protection Branch of the federal government has recently recommended a set of generic terms for insulin products similar (but not identical) to the "USP" designations (Appendix A). The rationale and extent of the "no-substitution" clause in government-sponsored formularies is undoubtedly variable and the scientific basis of these restrictions perhaps requires examination.

G. Conclusions

In general, given the likely continuation in the forseeable future of the subcutaneous route of insulin administration, the research community should be encouraged to seek better methods of improving the bioavailability of insulin, and of matching insulinemia to postprandial glycemia and exercise. Further rationalization of goals of therapy await clinical trials as to the nature of the interaction of hyperglycemia with microvascular complications. The pathophysiologic role of anti-insulin antibodies in the fetus of the pregnant woman with diabetes, and in relation to beta cell function in newly-diagnosed Type I (and possibly Type 2) patients should be further clarified, in order to rationalize the indications for highly purified, or synthetic, insulin pharmaceuticals. Improved methods of diagnosis of Type 1 as opposed to Type 2 diabetes, and improved methods of treatment of Type 2 diabetes, could potentially reduce the volume of insulin required and presumably be a cost-saving advance.

Modernization of the method of assigning potency would permit more precise comparisons of clinical and pharmacokinetic effects among the various preparations. Evolving studies of insulin pharmaceuticals in terms of antigenic and other characteristics should focus carefully on the roles of zinc, protamine, buffer content, as well as polymerization of insulin. Clearly there would be some advantage in reducing the number of preparations in the formulary, but until clear superiority is shown among the diverse clinical considerations encountered, it is likely that traditional formulations will continue (i.e. regular, Lente, protamine-bound insulins).

In the Canadian context there is undoubtedly a problem related to regional disparity of insulin supply, medical care and diabetes knowledge and expertise. These considerations bear not only of the problem of insulin administration, but all aspects of diabetes care.

The introduction and application by the medical profession of generic prescribing, and a rationale for permission to substitute, would be to the advantage of suppliers and consumers. Information suitable for decisions with respect to interchangeability of formulations should be agreed by the medical-scientific community and supplied by manufacturers. The stimulation and encouragement to the Canadian diabetes scientific community of a Canadian insulin manufacturing facility should be recognized.

A survey of the qualifications of physicians responsible for the treatment of insulin-requiring diabetes in Canada should be undertaken in order to rationalize strategies for further education, which would presumably enhance the application of appropriate insulin formulations to particular clinical problems, and increase the rate of attainment of treatment goals in the Canadian diabetic population.

H. Recommendations

1. Therapeutic strategies designed to maximize the advantage and efficacy of the various insulin preparations should remain under constant review from the clinical and scientific community.

2. A standard terminology for insulin pharmaceuticals should be developed jointly among the medical-scientific community, manufacturers and government.

3. A formula to permit consultation between scientific and clinical communities and insulin manufacturers with respect to the withdrawal and introduction of insulin pharmaceuticals in the Canadian market.

4. While a competitive insulin market should be encouraged among manufacturers, the advantage of an "on shore" manufacturing facility should be recognized in terms of encouragement of scientific enterprise, stability of pricing, and long-term availability.

5. Canadians should encourage and certainly be represented in proceedings related to revision of the method of calculating insulin potency.

6. Insulin utilization and prescribing patterns should be examined in relation to strategies for continuing medical education.

Acknowledgements for assistance are due to Mr. W. Ramsey, Dr. C. Burge, Mr. J. Witchert, Ms. T. Vanderschoot, Mr. R. Podsiadlo, Dr. R. Chance, Dr. W. Dorrington, Mr. R. Campbell, Dr. J. Davidson, and Ms. C. Solly for preparing the manuscript.

APPENDIX I

PROPER NAMES OF INSULIN PREPARATIONS

U. S. P. (1985)	ALTERNATIVE(S)	PROPOSED FOR CANADA
Insulin Injection	Regular Insulin Toronto Insulin	Insulin Injection
Prompt Insulin Zinc Suspension	Semilente Insulin	Insulin Zinc Suspension - Rapid
Isophane Insulin Suspension	NPH Insulin Isophane Insulin	Insulin Isophane
Insulin Zinc Suspension	Lente Insulin	Insulin Zinc Supension - Medium
Protamine Zinc Insulin Suspension		Insulin Protamine Zinc
Extended Insulin Zinc Suspension	Ultralente Insulin	Insulin Zinc Suspension - Prolonged

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PREGNANCY AND DIABETES

Anne Kenshole, M.D.

Introduction

Pregnancy in the diabetic woman is classified as a High Risk Pregnancy. Although the outcome for mother and infant has been steadily improving since the discovery of insulin, all diabetic women undergo an intensification of their metabolic abnormalities during pregnancy and women with established micro- or macro-vascular complications are at risk of transient or permanent worsening of their vascular status. In spite of an improved understanding of the pathophysical management of pregnancy, the diabetic woman remains at increased risk of developing toxemia, polyhydramnios and ketoacidosis. The fetus and infant of the diabetic mother continues to have a higher incidence of congenital anomalies, prematurity, neonatal morbidity and perinatal mortality (1). Follow-up studies on these children, however, have shown that they subsequently develop normally - physically, intellectually and behaviorally (2).

Pregnancy is a diabetogenic event and in 5% of pregnancies gestational diabetes develops. This is defined as transient diabetes induced by the altered metabolic milieu of pregnancy in a woman with compromised beta cell reserve. Although the degree of metabolic disturbance induced is usually subtle there is an increased risk of fetal macrosomia with attendant neonatal morbidity, and intrauterine death. Thirty percent of women with gestational diabetes will develop overt diabetes within seven years and sixty percent will become permanently diabetic within fourteen years of this diagnosis.

With respect to the delivery of health care, diabetic pregnancies result in increased interface with health professionals, an increased rate of hospital admissions and prolonged length of stay when compared with normal pregnancy.

PART I - Rationale for Management Plan

Over the past decade there has been an improved understanding of the metabolic changes that occur in a normal pregnancy as well as the specific changes that occur in pregnancy in the diabetic (3). Metabolically, pregnancy is characterized by accelerated starvation, facilitated anabolism, a state of relative insulin resistance induced by enhanced secretion of hormones, chiefly human placental lactogen, increased degradation of insulin, increased utilization of nutrients, a decline in the fasting plasma glucose and a 2-3 fold increase in insulin secretion by the maternal pancreas. In the diabetic woman, all these changes must be accommodated for by appropriate changes in her daily regimen. Inadequate adjustment can result in significant maternal and fetal hypoglycemia or sustained maternal and fetal hyperglycemia and/or ketosis and ketoacidosis. There is no clear cut evidence that fetal hypoglycemia is harmful though an association between first trimester major hypoglycemia and fetal anomaly has been suggested. Fetal hyperglycemia, however, is believed to result inevitably in fetal hyperinsulinemia with resulting macrosomia with attendant risk of birth trauma and neonatal hypoglycemia which can cause neurological damage. Maternal ketosis has been identified as a cause for sub-optimal intellectual development in the child and the development of ketacidosis in pregnancy adversely affects fetal survival.

A three to four fold increase in the rate of congenital abnormalities in babies of insulin dependent diabetic mothers has been recognized. Often these are major anomalies of the cardiovascular or skeletal and neuromuscular systems, frequently incompatible with life or resulting in life-long incapacity. Evidence has now accrued, especially over the past decade, that this excess rate of congenital abnormality can be normalized if maternal glycemic control is optimal at, and shortly after, the time of conception (4). It is thought that even brief hyperglycemia occurring at critical "windows" in the first seven weeks after conception may result in anomaly. When glycosylated hemoglobin is elevated above the norm, impaired oxygen delivery to the tissues occurs and this is one presumed mechanism by which such anomaly may result. It is highly desirable therefore that conception should occur only when it is known that the woman's glycosylated hemoglobin is in, or as close to, the normal range as can be achieved with meticulous adjustment of her diabetic regimen in the weeks or months leading up to conception.

There are conflicting data as to the impact of duration of maternal diabetes and the presence or absence of maternal vasculopathy on the risk of congenital anomaly.

The impact of pregnancy on the maternal vascular system is significant. The increase in cardiac output, circulation volume and the glomerular filtration rate that occur physiologically jeopardize the function of these systems in the woman with established vascular disease. Background retinopathy is common after ten years of insulin dependent diabetes and almost universal by twenty years. There is no evidence at this time to show that permanent worsening occurs as a result of pregnancy though transient increase can occur. There is conflicting evidence as to the effect of pregnancy on neovascularization, and as intensification of this potential threat to vision may be seen in pregnancy, some authorities recommend deferring, termination or avoidance of pregnancy in this setting (5).

Pre-existing maternal nephropathy and/or hypertension will predictably intensify with pregnancy. In addition there is an increased incidence of toxemia in this setting. Whereas the increase of proteinuria induced by pregnancy may ultimately revert to pre-pregnancy levels, there may be permanent worsening of the glomerular filtration.

The Role of Fetal Monitoring

Early growth delay may be shown on serial ultrasound evaluation in the first trimester in diabetic pregnancies. The significance of this observation is not yet known.

Serial ultrasound in the second trimester is a useful guide to the establishment of gestational age and timing of delivery. It may also detect fetal abnormality, early macrosomia and polyhydramnios before these are clinically detectable.

Regular assessment of placental adequacy and fetal well being is of ever increasing importance throughout the third trimester. Heavy reliance is placed on non-invasive techniques. The non-stress test (6), in which the fetal heart rate pattern is analysed, has become the standard way of confirming placental adequacy for ambulatory as well as in-patients. This has replaced measurement of urine estriol levels in most centres. Amniocentesis for measurement of lecithin/sphingomyelin ratios, an assessment of fetal lung maturity, is used routinely in some centres but only when gestational age or pulmonary maturity is in doubt in other centres. X-rays of the distal femoral epiphysis of the fetus as a way of estimating maturity should no longer be performed.

Timing of Delivery

The development of newer techniques of fetal monitoring has resulted in a significant change in the timing of delivery of these patients. A decade ago delivery at 35 or 36 weeks was traditional. Five years ago delivery was planned at 37-38 weeks and, now, many authorities are recommending that delivery can be carried out at 39 or 40 weeks if no obstetric or medical considerations supervene (7). This change has resulted in a lower incidence of prematurity, neonatal morbidity and a lower rate of Caesarean section plus a marked reduction in length of hospital stay, particularly for the neonate.

Outcome

Analysis of studies carried out over the past decade yields the following figures:

Stillbirths	3%
Perinatal Mortality Rate	0.9-6%
Congenital Anomalies	0-9%
Macrosomia	16-24%
Neonatal Hypoglycemia	2.7-31%
Caesarean Section Rate	45-54%

Mean Gestational Age at Delivery 38 wks.
Hydramnios 16%
Respiratory Distress Syndrome 8-11%
Toxemia 7-30%
(7,10,11,12,13)

In general these rates have tended to decline over the decade, the rate of complications declining as target blood sugars were successively lowered to the physiological range.

PART II - The Management of Pregnancy

The management of pregnancy in the known diabetic can be divided into five phases. Because of the complex nature of its management, it seems advisable that whenever possible the diabetic woman should be managed in a centre where the appropriate expertise and facilities are available.

PHASE I - Preconception

A. **Assessment of vascular status** This should include fundoscopic assessment through a dilated pupil and 24-hour urine measurement of creatinine clearance and protein excretion. From this assessment the risk of the woman can be established and in need the recommendation made to delay pregnancy until appropriate treatment has been received.

B. **Assessment of glycemic control** using glycosylated hemoglobin. Many centres now recommend delaying pregnancy until optimal glycemic control has been achieved in each individual.

C. **Optimization of Control** It is uniformly accepted that 'tight' control of diabetes, that is, obtaining and maintaining blood glucose levels as close to the norm as possible, is highly desirable throughout pregnancy. To attain this the patient must be competent in home blood glucose monitoring, usually require two or more injections of insulin daily, and must be able to adjust her own insulin doses on a frequent basis as indicated by the result of home blood glucose monitoring. She must also know how and why to test for ketonuria. Target plasma glucose levels are: fasting and premeal 5.5 mmol/l, post-prandial 6.6 mmol/l (8).

D. **Education** For the woman to be competent and confident in her own self- management it is critical to a successful outcome that a clear understanding of the goals and methods of achieving these goals is understood. Access to an informed health team, including a dietitian, a nurse and a physician, as often as necessary for each individual's requirement, is mandatory.

PHASE II - Early Pregnancy

If pre-pregnancy evaluation and education have not taken place, this should be implemented without delay. Often a brief hospitalization to expedite this is required in contrast to pre-pregnancy evaluation which can usually be achieved in the ambulatory setting. A team concept is encouraged with the patient taking responsibility for frequent blood and urine monitoring, control of dietary intake and adjustment of insulin doses. The physician follows glycosylated hemoglobin on a monthly basis, oversees appropriated insulin adjustment and establishes validity of home blood glucose monitoring technique, documents weight gain, follows blood pressure and renal status. Routine care is undertaken by an obstetrician versed in the management of these patients. Serial ultrasound is obtained on three occasions in the second trimester.

The patient is seen monthly in the first trimester, then three-weekly in the second trimester by the health care team.

PHASE III - Late Pregnancy

This is characterized by rapid metabolic change and obstetrical complications are more likely to intervene. The patient is seen twice weekly and ultimately each week. Non Stress Tests are initiated at 32 weeks, initially on a weekly basis and then bi-weekly. Hospitalization should be implemented without delay if medical or obstetrical complications develop. If previous intrauterine death has occurred it is advisable to hospitalize the patient before that gestational age for psychological as well as obstetrical reasons.

PHASE IV - Labour and Delivery

The gestational age at which hospitalization will be implemented varies from individual to individual. If no medical or obstetrical considerations supervene, admission can be delayed to near term. Frequently, however, earlier admission is advisable so that daily monitoring can more readily be performed and to ensure that blood sugars are kept in the normal range at a time when insulin requirements may be falling as placental maturation occurs.

The decision to deliver is made jointly by the physician, obstetrician and neonatologist/pediatrician. The time and route of delivery are predicated on the gestational age, maternal and fetal status. Caesarean section is no longer advocated as a routine and the majority of deliveries are now vaginal. The use of an intravenous insulin infusion to cover labour and delivery has become widely accepted allowing titration of glucose and insulin requirements independently to maintain the blood glucose within the physiological range and avoidance of ketosis throughout labour and delivery (9). Following delivery many women require no insulin for a period of a few hours or days. Insulin therapy should only be reinstituted when rising glycemic levels indicate its need. A rapid return to prepregnancy insulin requirements is common.

PHASE V - Postpartum

Even when optimal management of the pregnancy and delivery has occurred the fetus is still vulnerable and should be managed in a specialty unit where the appropriate monitoring devices and expertise are available. With optimal control however, these infants often "graduate" to the regular nursery 24 hours after delivery.

Nursing is encouraged to favour bonding. It has been suggested that development of normal maternal-infant bonding may be hampered because of the high levels of anxiety traditionally associated with pregnancy and childbirth in diabetic women.

Some relaxation of tight control after delivery is to be expected and is permissible, but frequently women who have experienced the benefits of tight control throughout pregnancy, often for the first time in their diabetic lives, choose to maintain an enhanced level of control thereafter.

GESTATIONAL DIABETES

Gestational diabetes occurs in 5% of pregnancies. Risk factors include maternal age greater than 30 years, maternal obesity, and a significant family history of diabetes. It should be sought for when pregnancy has previously resulted in intrauterine death, in cases of repeated mid trimester stillbirth, a history of glucose intolerance at any time previously, when glucosuria is detected during pregnancy, polyhydramnios, hypertension, and when macrosomia is detected.

It is recommended that all pregnant women be screened at 24-28 weeks of pregnancy using a 50 gram glucose challenge (8). Normal values are Fasting - 5.8 mmol/l two hours after a meal or challenge, less the 6.6. mmol/l. When a high index of suspicion exists, as noted above, a screen should be performed once in each trimester. If borderline results are obtained a glucose tolerance test utilizing a 100 gram challenge should be given.

The result is considered abnormal if two or more readings equal or exceed the following:

Fasting	5.8 mmol/l (plasma glucose)
1 hour	10.5 mmol/l
2 hours	9.2 mmol/l
3 hours	8.1 mmol/l

Management is as for the insulin dependent diabetic. All patients should be started on a diabetic diet, modified for pregnancy needs. No attempt should be made to achieve weight reduction during pregnancy. Regular monitoring of glycemic levels preferably by home blood glucose monitoring is required. The role of insulin use as a routine remains controversial. There is some evidence that suggests that the incidence of macrosomia is lower with its routine use, but most authorities continue to recommend institution of insulin only when target blood glucose levels cannot be maintained by diet alone. It is recommended that human insulin be used because of its low immunogenic potential.

Fetal monitoring as for the insulin dependent diabetic is recommended because of the known association of gestational diabetes and intrauterine death. Gestation should not be continued past 40 weeks.

Most women with gestational diabetes will have regained normal glucose tolerance within one week after delivery. A glucose challenge should be given within the first few weeks after delivery. Gestational diabetes commonly recurs with each successive pregnancy.

Type II Diabetes

This is relatively uncommon in the childbearing years. Oral agents should be discontinued prior to conception because of possible teratogenesis, and if acceptable glycemic control cannot be maintained on diet alone, insulin should be started and the patient managed as an insulin dependent diabetic throughout the pregnancy.

PART III - The Canadian Scene

An informal network of internists and obstetricians interested in this area exists and the views and concerns of several are incorporated in this document. Their input is gratefully recognized. It should be emphasized, however, that patterns of practice in large urban centres do not necessarily reflect the situation in smaller, especially remote, communities.

There appears to be universal acceptance of the significance of pregnancy in the diabetic. The goals and methods of management are broadly similar in all centres contacted.

Centralization of care varies considerably. In large cities such as Toronto and Montreal, patients are cared for in many different hospitals, by virtue of the numbers seen. Though an effort at standardization of care between institutions has been attempted it remains incomplete. In medium sized cities such as Quebec City, London, Ottawa, Winnipeg and Calgary, it appears that centralization has been more effectively established despite the difficulties inherent in distance of travel.

Standards of practice in small communities appear to reflect the awareness and expertise of the local health care team.

Objective data concerning outcome have proved difficult to access. At the federal level no data bank exists or has been discovered; Statscan merely identify maternal mortality associated with diabetes (zero cases in 1983) and neonatal mortality attributed to "IDDM" (three cases in 1983). This latter figure is obviously misleading as the primary cause of death, for example respiratory distress syndrome, congenital anomaly, etc., would usually be identified as the actual cause of death, in these infants.

Provincially, different mechanisms exist for retrieval of health care statistics. Although an international standard code of disease classification is used throughout, differences in data gathering appear to make interprovincial comparison difficult.

Published data from Canadian centres are scanty, perhaps reflecting the rather recent move towards centralization. Unpublished figures, however, reveal that maternal and fetal outcomes in the larger centres generally reflect the improvement documented in the worldwide literature.

No data as to management and outcome in the rural or remote settings exist.

Part IV - Recommendations

A. General Recommendations

1. Recognition

Recognition of the significance of pregnancy and diabetes from the preconception phase onwards should be disseminated throughout the population at risk and the health care professions.

2. Education

The (a) public at large, (b) population at risk, (c) health professionals, especially those in non-urban practice, (d) health care professionals in training require education and repeated re-education as new information becomes available in this area. Vehicles for this include the media, literature published by the Canadian Diabetes Association, the Juvenile Diabetes Foundation and some pharmaceutical companies, diabetes education centres of which there are over one hundred in Canada and programs for continuing medical and health professional education. In that a rather low percentage of people with diabetes in Canada belong to the Canadian Diabetes Association or Juvenile Diabetes Foundation, the use of the media to reach the target population as well as the population in general, seems advisable.

3. Stratification

With improved dissemination of information and management it should prove possible, on a cost-benefit basis, to stratify these patients into those who can be managed at a primary care, as opposed to a secondary or tertiary care level. For example, the gestational diabetic should be manageable in a primary care setting whereas the insulin dependent diabetic usually benefits from referral to a centre where the appropriate expertise is concentrated. Those patients whose medical or obstetrical status requires a higher level of sophistication should have ready access to a tertiary care centre.

4. Centralization

The development of centres of excellence for clinical care and for research is desirable. This should include not only large urban areas but should be developed in small towns on the basis of geographical logic, as has been attempted with the development of perinatology centres. It should be possible to locate these centres so that the majority of patients would be within one or two hours driving time.

5. Economic Considerations

The use of home blood glucose monitoring is virtually universal in the modern management of diabetes and pregnancy and the improvement in outcome that has resulted is unquestioned. The cost of frequent monitoring is high and is usually borne by the patient alone or with third party coverage. Provincial reimbursement of costs varies greatly from the hundred percent coverage afforded patients in Prince Edward Island to Newfoundland, where financial assistance is only available to seniors and those on welfare. Because of their superior accuracy the use of reflectance meters is recommended rather than visually read strips and the cost of these meters, from $100-200, plus the costs of the strips which are approximately 60 cents each, puts home blood glucose monitoring beyond the reach of a significant number of patients who would benefit from this. As a result, several centres now have meters that can be rented or loaned to the patient for the duration of their pregnancy. A federal or provincial program for purchasing or loaning meters and underwriting the cost of strips is desirable.

Pregnancy is one of the more widely accepted indications for continuous subcutaneous insulin infusion (CSII) because of the superior glycemic control it can provide. The cost of these devices ranges from $1,000 to $2,500 and the cost of disposable equipment including home blood glucose monitoring, is estimated at between $50-150 per month. Although some insurance companies will now underwrite some proportion of these costs in this setting, it is not universal and the cost continues to limit application of this technique. A centrally underwritten loan program managed through the tertiary care centres identified above is recommended. In that the Province of Ontario is understood to have accepted in principle the underwriting of costs of home blood glucose monitoring, for the 18 year old and under patient, it is recommended that a similar program be implemented, Canada-wide, for the pregnant diabetic woman.

6. Development of a Registry

It is apparent that a significant lack of data currently exists including such fundamental information as the number of pregnancies among diabetic women each year in Canada and their outcome. A register exists in Prince Edward Island and its use is well established in Denmark and Czechoslavakia among other countries. The development of a register is being pursued in the United States.

7. Research

The answer to some fundamental questions remains elusive. For example, the cause of sudden intrauterine death, the genesis of macrosomia, the need for insulin in the gestational diabetic and the impact of pregnancy on neovascularization of the retina. With the universality of health care enjoyed in Canada a more representative picture can be obtained in clinical research than in countries where socioeconomic factors impact more markedly on delivery of health care, and so Canada should be able to make a significant contribution to world experience. The expansion of the already existing network encompassing tertiary care centres should enhance cooperative interdisciplinary research.

B. Specific Recommendations

1. Validation of criteria for establishing the diagnosis of gestational diabetes. No uniformity exists as to the use of screening procedures of the oral glucose tolerance test in pregnancy. In that it is recognized that even modest elevations of glucose can adversely affect fetal development, validation of currently used tests, followed by recommendations for uniform application, is urgently needed.

2. Information transfer. Because of the frequent contact that is necessary between the patient and members of the health care team, it is desirable that a series of "hot lines" be set up so that frequent telephone contact may be maintained, especially where geographic considerations pertain.

3. Preconception Assessment. Many centres continue to offer comprehensive management after the diagnosis of pregnancy is established. Few as yet are emphasizing preconception management.

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MANAGEMENT OF INSULIN-DEPENDENT DIABETES IN CHILDHOOD

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Type 1 or insulin-dependent diabetes mellitus (IDDM) has an incidence of 10-16 cases/100,000 population/year, leading to a prevalence of about 1 per 600 children below the age of 20 years (1). This makes it the most common and perhaps complex endocrine-metabolic disorder in childhood.

The etiology of IDDM remains obscure: prevention and cure remain elusive despite extensive ongoing research (2,3). Therefore, for the foreseeable future, therapy for IDDM will probably continue to depend on the maintenance of adequate glucose homeostasis (control) by the delicate balance between insulin administration on the one hand, and performance of the daily routines (diet, self-monitoring of blood and urine, exercise) on the other. This balance depends to a great degree on:

1. the acquisition of self-care skills emphasizing the need for patient/family education and updating; and
2. psychosocial factors - i.e. the impact of diabetes on the child/family.

This analysis of management issues in the child with IDDM is predicated on the acceptance of two major issues:

1. that diabetes is an important cause of morbidity and mortality. This has been well documented, for example, in the United States where 2.4% (over 6 million people) of the population are affected, resulting in direct and indirect costs of more than $9.7 billion/year (4); and

2. that the problems of the child with IDDM are sufficiently distinct from those of the adult (e.g. supervision, growth and development, need for a developmentally structured approach to education, parent-child interactions, etc.) to warrant special attention (5-10).

This paper will attempt to analyze:

1. the "ideal" approach to diabetes management in children as it relates to government, physician/hospital, and parent/family responsibilities and involvement;
2. the current status of childhood diabetes management in Canada. This analysis will lead to some recommendations for improvement in the system(s) as it exists in Canada. The discussion, however, will not provide an in-depth debate on the controversy regarding the relationship between metabolic control and the complications of diabetes since this is the subject of major ongoing research (11,12). Rather, it will accept the basic premise that therapy should aim to achieve the best possible glycemic control in each

individual child; a proviso being that this therapy does not expose the child to any more than mild, occasional hypoglycemic episodes that are readily recognized and treated and do not interfere with daily living (13-21).

STATE-OF-THE-ART

Aims of therapy

Traditional therapeutic goals are those long established as essential for the treatment of diabetes and include:

1. abolition of symptoms of hyperglycemia,
2. avoidance of severe hypoglycemia,
3. avoidance of ketonuria,
4. maintenance of normal growth and physical maturation,
5. promotion of physical and emotional well-being,
6. minimization of urine glucose losses, and
7. maintenance of normal blood lipids (5,6,13,14).

Emerging goals are those that are developing as our understanding of diabetes and our ability to control it are increasing, and include:

1. achievement of normal or near normal blood glucose levels, particularly before meals, and
2. decrease in HbAlc levels to as near the non-diabetic range as possible (22-26).

Setting of therapy

It is clear that the management of children with diabetes is too complex to handle solely on a medical basis (5,8). The child and his/her family bear the constant life-long responsibility for the day-to-day management of diabetes.It is obvious that this is a particularly heavy burden. The children must learn not only to accept this burden of being "different" from their friends, but also how to integrate the pressure of the diabetes regimen with those of daily living (family, school, extracurricular activities, etc.) (7,14).

As a result of these pressures, the concept of the multidisciplinary health care team has arisen (7,8,27-32). Such a team would be expected to comprise

1. a physician or physician(s) (preferably a pediatrician trained and experienced in the care of children with IDDM): leadership of the team is of necessity in the hands of the physician since it is he/she who accepts ultimate responsibility for patient care;
2. nurse educator(s)/coordinator(s);

3. nutritionist (dietitian): it is essential that these people be experienced not only in the dietary needs of the diabetic child but also of infants and of the nutritional requirements of growing children;
4. behavioral personnel - social worker, psychologist, psychiatrist. Wexler (28) has reviewed the role of the social worker in great detail;
5. public health nurse - to provide a life-line between hospital/clinic and home;
6. community support groups, e.g. parent support groups; and
7. the child/family unit must become an integral part of the team not only to feel more directly involved in the diabetes care, but also to help define the specific needs of their particular unit.

The role of the team is to provide **consistent** and complete support for the child and family in order to help them to cope with specific tasks:

1. **Cognitive-practical tasks**
   (a) understanding the medical facts, and developing an accurate perception of diabetes and its short- and long-term effects (cognitive);
   (b) learning about and experiencing diabetes care (practical);

2. **Psychosocial tasks**
   (a) coping with the impact of the diagnosis;
   (b) coping with the changes attendant upon this diagnosis and working through the emotional distress caused by both the impact and consequences of the diagnosis;
   (c) experiencing a sense of control over IDDM thereby helping to maintain good self-esteem;
   (d) starting to develop a realistic acceptance of diabetes with positive and realistic short-term and long-term goals.

It almost goes without saying that the education/understanding process takes a great deal of time and warrants continued reinforcement and updating. Along with this, the adjustment process is a slow one progressing through the early impact phase to the learning and doing phase, the integration phase and finally to long-term coping. (28)

The ideal situation would be for each child/family unit to have routine and easy access to a multidisciplinary health care team. These teams are, however, large and therefore costly and, of necessity, concentrated in centers with a big enough patient load to warrant such a team, i.e. usually larger cities with university teaching hospitals. This means that families from rural areas and smaller towns and cities will not have the same access to the team members as those living in close proximity to the hospital/clinic. For the latter, local family physicians/pediatricians are needed to bridge this gap. In the major pediatric centres, diabetes education and ongoing care are inextricably bound. This differs from most adult centres where the sheer weight of numbers necessitates separation of education and care. In those areas where this separation also affects children with diabetes, it is important for primary care physicians to be fully conversant with the education program and treatment goals of the referral centre to which he/she sends these children.

Of major importance in the care/education follow-up routine is that members of the team be consistent in their approach to the individual child and his or her family. Thus to function properly, the team needs (1) an identified leader (physician); (2) an overriding philosophy of care and education; and (3) frequent contact of team members to discuss individual cases (7,8). The team needs to maintain close contact with the primary care physician of the particular family especially when the child lives a distance from the hospital. Furthermore, a team member must be available at all times to deal with acute problems, e.g. hypoglycemia, diabetic ketoacidosis (DKA), intercurrent illness (30).

Ideally, the care/education program by the multidisciplinary team should begin at diagnosis. For most children, a period of hospitalization is required for stabilization and initiation of therapy. The duration of and even the need for hospitalization have been debated (7,8,33a,33b). The education plan requires a stepwise approach, always bearing in mind the need for continuing learning to review basic concepts of the disease, transmit new knowledge, and stimulate ongoing involvement/interest in the maintenance of good self-care routines (control)(8). The depth of the educational process must be tailored to the individual needs and abilities of the family (14). It is a distinct impression that the quality and quantity of the initial education program is of prime importance in the successful establishment of good metabolic and psychosocial adjustment.

Successful management of children with IDDM includes knowledge of:

1. appropriate use of insulin,
2. nutritional planning,
3. exercise and its effects on diabetes,
4. emergencies such as hypoglycemia and intercurrent illness and how to handle these.

How successful are multidisciplinary diabetes health care teams in achieving the aims set out above? Although most patients and team members attest to the efficacy of the team approach to diabetes care and education, the literature is not replete with data on this subject. The available data however are positive. Some examples include:

1. Deckert et al (Denmark) demonstrated that the prognosis of IDDM (assessed by mortality relative to a non-diabetic population and by prevalence of complications such as retinopathy and nephropathy) is significantly better in those patients who frequently attend versus those who are only in sporadic contact with the clinic (12).

Furthermore, they documented the cost-effectiveness of this improvement to be over $100,000 per patient over the 40 years of their study (34).

2. In Israel, Laron et al (7) compared their results before and after inception of a multidisciplinary treatment scheme for diabetic children. They concluded that the team approach had the following positive influences: the degree of control attained was both higher and sustained with greater regularity; there were fewer short-term complications (e.g. DKA, coma, brittle diabetes) and almost no need for repeat hospitalization; the attitude of the child, parent and teachers was found to be improved (less absence from school, etc.); there was better understanding of the disease and its requirements; the child's self-concept was much higher. The assessment of each of these aspects, however, was based on fairly subjective criteria.
3. Hardie et al (31) show a significant decrease in the hospital admission rate of diabetic children after introduction of a children's diabetic clinic in Oxford. This was due mainly to a decrease in admissions for severe DKA.
4. Hoffman et al (30) in Detroit reported on a pilot program of service and education designed to involve an inner-city, insulin-dependent diabetic group of children actively in their own diabetes management. Included in this program was a 24-hour telephone "hot line" for questions and advice. The clinic population increased over a 4-year period from 80 to 147 children while admissions per year declined from a total of 48 to 8 per year (more than 80% decline). The decline in admissions was noted within 1 month of establishing the service. The estimated cost benefit was in excess of $100,000 per year.

Of note is that the benefit of such programs cannot and should not be measured in terms of cost effectiveness only. The benefits (immediate and long-range) in terms of preventing morbidity and mortality, allaying anxiety, etc., are likely to far outweigh the cost savings.

One caveat that is essential to discuss is the following: although the advantages of education for the person with diabetes are undisputed, the best mechanism for such a program remains debatable. For example Page and associates (32) studied 24 IDDM children: they were all interviewed immediately following a clinic visit to determine which of the recorded instructions delivered by the team members (physician, nurse educator and nutritionist) were recalled. The health care team recorded an average of 7 recommendations per patient (total 168 items). Patients recalled an average of 2 recommendations (total 50), 40% of which had not been recorded by the team members. It was concluded that an understanding of the communication process is necessary if self-care instructions are to be successful. Also a valid pre- and post-test must be part of assessment of the educational program.

Government Responsibility

A variety of reports have suggested that substantial reductions in health-care utilization and costs can be achieved through more organized and intensive diabetes care, and, in particular, education activities. They also support the continuing need for public health agencies to be involved in organizing these activities (35-38).

The responsibility of government is therefore multifold and is to ensure that

1. uniform care/education is available throughout the particular jurisdiction/area;
2. properly trained personnel are available and that funding is available for training of more personnel to meet the needs of the particular community. This also implies that the personnel be adequately rewarded/paid for their services;
3. the considerable financial burden of diabetes care is removed from the patient/family.

Reimbursement

A major barrier to cost-effective preventative services for people with diabetes has been and continues to be the absence of reimbursement by government or third party insurers for quality out-patient education, diet instruction and counselling, and psychosocial support services. The studies cited above adequately indicate that such services, although costly, in fact reduce excess hospitalization, medical care and time off work/school.

Physician/Hospital/University Responsibility

That there is a paucity of programs and people available for diabetes care and education has been well documented (39-41). The National Commission on Diabetes of the US reported to the US Congress in 1975 giving evidence that the quantity and quality of diabetes education (and, by inference, care) was inadequate, e.g.

1. only half of the hospitals in the Minneapolis area had programs at the time;
2. a survey of 32 education centers revealed that they served only 0.05% of known diabetics in the United States (39).

A survey of services available at 123 Kentucky hospitals revealed that only 9 had a diabetic teaching nurse, 6 a diabetic nutritionist, 9 teaching classes and 3 social services (41). This is despite the fact that diabetes afflicts 4.4% of Kentucky's population, is the leading cause of hospitalization by disease and costs over $100,000,000 per year.

The record in Pennsylvania is similar (40): over 1/2 million Pennsylvanians have diabetes; 7% of all hospitalizations during 1980 were for a primary or secondary diagnosis of diabetes; total costs are $1.3 billion annually; of 280 acute care hospitals, only 17% have a full-time diabetes educator, 29% a part-time educator, and only 19% a diabetologist on staff. Furthermore of 24 physicians in the state who list diabetes as their specialty, 17 were located in the two largest cities, Philadelphia and Pittsburgh. These two cities are also the only ones with specialized diabetes programs for children.

Thus, once government can be persuaded to provide funding for programs, it is essential that the hospitals and physicians provide the necessary services. In the case of children with diabetes, the ideal is that, at diagnosis, they should be referred to a center specializing in diabetes management in these age groups. Where this is not possible, stabilization of metabolic control and education should be provided in the closest unit able to meet these needs adequately. These suggestions are consistent with those of the Canadian Diabetes Association (CDA) (42). Follow-up care is best provided in the same facilities to provide continuity and consistency of care.

In those communities distant from such centers, it is incumbent upon the local physician to remain in touch with regional experts and maintain a "current" awareness of diabetes management.

The responsibility of government through pediatric hospitals, therefore, is to direct the necessary funding for establishment of multidisciplinary health care teams dedicated to the care of children with diabetes. A further responsibility in the larger (university) centers would be to foster training of personnel to staff such teams. The concept of Diabetes Research and Training Centers in the United States offers an excellent model for such training.

Responsibility of the local primary care physicians would include awareness of:

1. regional facilities available for care/education of children with diabetes; and
2. current trends in diabetes management if they personally take responsibility for the overall care of these children.

A final responsibility is education of teachers who deal with children with IDDM on a daily basis. In one study, only 25% of teachers surveyed appeared to have adequate understanding of diabetes and very few had knowledge of diabetic emergencies (43).

The Child with Diabetes in Canada

A Special Report on Diabetes Mellitus by the CDA of February, 1982 (42) commented that "the clinical features, including the psychosocial aspects, of diabetes in young patients can be so different in young patients that it is necessary to comment separately on the management of adolescents and children". Specific strategies for management of this age group included the following statement: "Ideally at diagnosis all children and adolescents who develop diabetes should be referred to a center specializing in diabetes treatment and education of these age groups. Where this is not possible, the establishment of metabolic control and the necessary education should be carried out in the accessible unit best able to provide for these needs". However, there is precious little data documenting the details of care of children with diabetes in Canada.

It is clear that there is neither a uniform approach nor uniform facilities available across Canada for the care of children with diabetes. The large size of the country and relatively sparse population in certain areas make this close to impossible to achieve. At a government level, medical care is covered by health plans in all provinces, educational programs are generally unfunded throughout, while payment for diabetic supplies (insulin, syringes, self-monitoring equipment) varies from province to province (see Appendix 1).

An unpublished review of the status of diabetes education in Toronto by the University of Toronto's Banting and Best Diabetes Center documented the lack of organized hospital programs for diabetes education (and, by inference, care) in many of the city's hospitals.(9) Their conclusions no doubt reflect the extent of these deficiencies across Canada. In many hospitals, the report concluded, there is no structure, direction or coordination of programs, the most important reason being the lack of an involved and interested physician to provide leadership. A second problem identified relates to the lack of nurses and dietitians dedicated to diabetes care/education, since these are the key people required to implement the program. Other problems identified included lack of adequate space, and particularly, inadequate funding. Of 21 hospitals surveyed, only one has a multidisciplinary team specifically geared to the child with diabetes, while two others reported facilities for children within their "adult" programs.

The reports from the Diabetic Day Care Unit, McMaster Medical Center (33a,33b) documented improved control (in terms of frequency and in patients in severity of hypoglycemia and acidosis) in their program, whether on an in-patient or out-patient basis.

Multidisciplinary health care teams exist in most of the major university centers although their composition and cohesiveness appear to vary greatly. For example, one center with a small patient population, depends on part-time participation of a physician, nurse and dietitian, while in a larger center, a full-time team with more than one each of physician, nurse, dietitian and behaviorist is hard pressed to meet the needs of an expanding clinic population. Despite these teams, a significant percentage of newly diagnosed patients and their families receive their care and education in adult programs in smaller institutions unaccustomed to dealing with the specific problems of diabetes in childhood. Personal experience suggests that this latter group of patients can be divided into two subgroups:

1. those that live a considerable distance from a major pediatric center and receive care/education in the nearest available unit; and
2. those whose physicians feel that referral to a pediatric center is unnecessary. Many of these children "make their way" to the specialty clinics only when problems (eg. recurrent DKA, hypoglycemia, psychosocial problems) supervene.

The Directory of Diabetes Education Services in Canada (prepared by the C.D.A., December, 1983) reviewed available services in terms of (1) full-time versus part-time facilities; (2) in-patient and/or out-patient education; (3) preassessment, dietary history, program focus (group versus individual), evaluation and follow-up; and (4) team composition. There was not a specific category targeting care/education of children with diabetes. Nevertheless, of 11 children's hospitals included, 9 reported they have full time and 2 part-time diabetes services; all involved both in- and out- patients; 8 included a preassessment; 10 a diet history; all individual instruction and 2 groups as well. Seven of the teams included an M.D. advisor, a registered nurse (R.N.), nutritionist (R.Dt.) plus other personnel (eg. social worker, psychiatrist), while 3 had only M.D., R.N. and R.Dt., and one only an M.D. and R.Dt. However, the specifics of each program were not outlined.

The philosophical approach to, and facilities available for, diabetes care also vary greatly. For example in most centers, self-monitoring of blood glucose and glycosylated hemoglobin measurement are a routine part of care/education. However, there are certain areas where urine testing remains the routine form of self-monitoring, and glycosylated hemoglobin measurement is unavailable. Similarly, in some centers, 24 hour "hot line" telephone numbers are available for crisis intervention, in others, and particularly in more rural areas, both chronic and acute care is the responsibility of the family physician or local pediatrician. Acute problems in such settings morefrequently require emergency room attendance and hospitalization.

Patient educational aids are available both locally, eg. diabetes care manuals of the Hospital for Sick Children, Toronto and Montreal Children's Hospital, and nationally through the Canadian Diabetes Association and other support groups. Parent support groups exist in some areas and their organizations vary considerably, eg. allied to CDA or Juvenile Diabetes Foundation (JDF) versus independent groups.

Professional education of primary care physicians, internists, pediatricians and other medical personnel who come into (frequent) contact with diabetic children is truly a hit and miss affair.

Certainly there are continuing medical education symposia on diabetes as well as a multitude of journals, etc. dealing with current diabetes therapy. The impact of these resources on professional education is uncertain.

There would also appear to be a paucity of Canadian pediatricians presently pursuing careers in diabetes in childhood, as well as a lack of guaranteed government funding for such training.

In summary, it is probably true to state that the care of children with diabetes in Canada is excellent where these children have ready access to specialty clinics with multidisciplinary health care teams available for acute and chronic care and declines as this access is lessened, unavailable or withheld.

Recommendations

The Pennsylvania Diabetes Task Force has established six elements in their Pennsylvania Diabetes Plan. These were selected because they have been shown to reduce diabetes morbidity, mortality and costs (42). These key elements are:

1. **Patient care/education:** Currently, both the quantity and quality of diabetes education are inadequate. This is perhaps the top priority need.
2. **Professional education:** There is a feeling that significant clinical information regarding recent advances in diabetes management has not reached large numbers of primary health care providers who, in the United States for example, treat 80% of all diabetes.
3. **Adequate reimbursement** has been discussed.
4. **Linkage with other programs** is essential since diabetes affects virtually every organ system in the body and impacts upon many health service programs, eg. vision, pregnancy, hypertension, etc.
5. **Complication-specific activities** to reduce morbidity and mortality. This implies availability of specialists expert in the care of retinopathy, nephropathy, etc.
6. **Communication** of activities available and new development is also essential both to the patient population at large and community medical practitioners.

From the discussion above it would seem appropriate that the following recommendations should be made regarding the care of children with diabetes in Canada.

1. Accurate information should be obtained regarding the levels of care across the country, in both urban and rural areas. This could be done by surveying university pediatric departments, community pediatricians and family physicians.

2. Standards and guidelines for care of children with diabetes should be set. This could best be achieved by a workshop/conference of pediatric diabetologists, nurse educators, dietitians and behavioural scientists.
3. The setting of professional education goals should be part of the workshop suggested in 2. This could be in the form of a position paper/booklet on the optimal standards of care and education for children with diabetes.
4. The workshop participants or their representatives should meet with federal and provincial government representatives to lobby for funding of programs aimed at improving various aspects of care, e.g. payment for patient supplies (insulin, syringes, monitoring equipment, etc.), adequate reimbursement for services and, funding for the training of the personnel needed.

Conclusions:

This paper has reviewed the need for specialized care for children with diabetes. The advantages of such care/education would appear to heavily outweigh the costs of the necessary programs. The status of childhood diabetes care in Canada is uncertain and likely to be quite variable.

Laron put the problem in perspective in 1970 when he stated that "diabetes has very wide implications, and seems to present a very complicated picture. It seems certain that its rehabilitation needs a multidisciplinary team approach involving professionals, knowledge, good will and.....money" (44).

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EDUCATION

EDUCATION IN DIABETES MELLITUS
SUMMARY AND RECOMMENDATIONS

Learning and Diabetes - Alan Thomas

A major recent development has been our ability to distinguish between learning and education. Education has been associated with the imposition of information, often of questionable relevance, by authority figures, this being resisted by many students on principle. The enforced acceptance of information is unlikely to change behavior in the student.

A change in behavior is required from diabetic patients to achieve and maintain good control. Learning, and behavior change require courage and determination to alter the previous comfortable responses that are part of the identity of any individual. The word treatment has come to mean that someone does something to someone else, but its original meaning was connected with "treaty", in which an agreement was negotiated, and treatment in this sense merges with learning. Adults learn mostly as a means of solving pressing problems, and they learn best from other adults whose experience they trust. Since learning involves change, these changes must be negotiated by the diabetic not only with health professionals, but also with family members and others in their social sphere.

The learning 'curve' is a misnomer, since learning follows a stair case pattern. New information or skills must be assimilated, which takes time. During this time new information is less useful or is not accepted at all, and what is required is rather encouragement, patience and support, with time and space to practice. Health professionals may fail to realize that learning is a highly individual characteristic, each person learning in a different way, and mostly unconsciously; some learn by teaching and doing; others by observing and deducing; others by seeing or hearing; and yet others by reading and reflecting. A teacher must assess the learning characteristics of each individual before teaching can be successful.

The management of diabetes requires a change in the classical relationship between doctor and patient. The concept of 'treatment' must be changed to 'treaty' and each of the partners must negotiate for change, which may be even more difficult for the health professional than the patient. It requires patience and skill to turn a patient into a learner, and health professionals must learn to become facilitators rather than didactic teachers, if they are to be successful educators.

Educational Issues in Diabetes Mellitus - Charles Clark

In 1974 the U.S. National Commission on Diabetes was formed, and charged with formulating a long range plan to combat diabetes. This was later reconstituted to form the National Diabetes Advisory Board to implement the long range plan to establish diabetes research and training centers, and there are seven such centres currently in operation. Diabetes control projects have been funded by the Centre for Disease Control in conjunction with 20 state health departments and the U.S. Indian Health Service also operates a number of model diabetes demonstration programs. Each centre is charged with specific areas of research in the development of behaviorally and clinically effective diabetes education models. Constant efforts are being made to improve the effectiveness of the education of diabetic patients.

A second objective was to introduce postgraduate and continuing medical education programs designed to increase the number of health care professionals skilled in the management of diabetes. It was shown that the crucial factor is not increased factual knowledge, but what is done with it. Only by adding audit feedback and precise guidelines to this knowledge was the control of diabetes influenced. Educational programs must include professional and environmental factors other than competence to result in better care and improved patient outcomes.

Research suggests that patient education is essential for effective management of chronic diseases such as diabetes. But while any education is better than none, behaviorally oriented patient education with an emphasis on self care was found to be up to three times more effective than didactic programs.

In 1978 the Diabetes Research and Training Centre (DRTC) at Indiana University developed a randomized, controlled trial of physician and patient education in the management of diabetes. It was shown that education of either physicians, patients, or both, improved the outcome in terms of blood glucose levels, hemoglobin A_{1c} and weight loss compared to the control group, and the best results were produced when both physicians and patients were educated independently.

A. Program for Adults with Diabetes - Jean Tyson

The presentation included the planning for organized programs which included models that dealt with both goals and objectives and the teaching facilities and programs. The presentation outlined prerequisites for the contents and planning of programs. An ideal model was outlined with emphasis on the practical approach to the practice elements of teaching skills. The incorporation of follow-up should be a key element in terms of the assessment of skills. The present situation is that 179 known centres exist in Canada providing a wide variety of programs.

Recommendations

1. Education should be accepted as an integral part of treatment.

2. Education should be multi-disciplinary.

3. Education should be publicly funded.

4. Education should be available to all Canadians with diabetes and their families.

5. Education should be given by properly qualified personnel.

6. Standards and guidelines should be developed and implemented.

7. There should be a review of existing education facilities across Canada.

B. Educational Programs for Children with Diabetes - Mimi Belmonte

Special characteristics of programs for diabetic children include the small number of patients who are involved, the need for individual teaching, the fact that all patients have type 1 insulin dependent diabetes, the requirements to deal with parents as well as patients who are growing both mentally and physically, the need to be cognizant of the life habits and family situation of the patients, and the concern as to when it is appropriate to give the children added responsibility.

Recommendations

1. All children should be cared for or receive regular review by a specialized team in a tertiary care facility.

2. The family should be involved in the learning process.

3. The goals of teaching should be directed to an understanding of the patho-physiology of diabetes by the patient and parents and that a major goal must be the establishment of new life habits in areas such as eating and exercise.

4. Education should be an ongoing process throughout the whole period that the child is under pediatric care.

5. An improved method for transfer of patients from pediatric to adult care should be developed across the country.

6. All programs should receive on-going evaluation.

C. Nutrition Education for People with Diabetes - Jan Eno

The presentation emphasized that the message taught is not necessarily the message learned and that generally people learn what they perceive is necessary. The Good Health Eating Guide cuts down on mixed messages, but an outside evaluation of this specific tool is needed. A distinction between diet counselling and diet education was made. Dietary knowledge at a survival level may take up to 5 hours of education time whereas to establish lifetime changes may take a minimum of 20 hours. Good diabetic self-care requires a knowledge of what, when and why dietary information must be implemented. Teachers must also take the time to learn how to effectively teach clients. Diet is crucial in the treatment of diabetes and proper funding in this area is critical.

Recommendations

1. Nutrition education and counselling should be essential components in the effective management of diabetes.

2. The health care system should provide adequate funding for nutrition education and counselling.

3. There should be an evaluation of the Good Health Eating Guide system.

4. Nutrition education should be part of any health care facility.

D. Education Assessment - David Surridge

A valid educational assessment must be based on what the patient does rather than on what the patient knows. To be successful education must be based on the 'whats', and not the 'whys', and an initial assessment of the patient's intellectual ability. Stress may be associated with behaviors which temporarily limit learning, and professionals must recognize and deal with these before learning can be reestablished. Certain specific areas cause stress in diabetics, including a delay in psycho-sexual development which appears to occur in adolesence, so that their psychological development may be delayed up to two years compared to physical development. Impotence in the male is another cause of stress. The educational process must acknowledge that there are situations in which other health problems take precedence and prevent successful education until they are solved. The need for professionals to consult with other individuals such as relatives or business associates to assist in the assessment of the patient was emphasized.

Recommendations

1. Psychological factors should be recognized as influencing the management of diabetes with respect to both education and adherence to a treatment program.

2. The Health Belief Model in each individual should be recognized as influencing learning and management.

3. Simulated tests and information from an informant should be used in preference to direct questioning for qualitative assessment of learning by the person with diabetes.

E. Program for Allied Health Professionals - M. Verroneau

The ideal situation for the training of allied health professionals was outlined in terms of defining the role of educators offering basic and advanced programs. Such training would include a multifacetted background, follow-up and evaluation, national resource bases, coordination of national workshops and continuing education models. The actual situation as it exists in Canada is far from ideal. The United States is making progress in terms of accreditation and teaching modules, and collaboration exists between Canadian allied health professionals and the American Association of Diabetes Educators.

Recommendations

1. A national agency should be established to coordinate a training program for diabetes educators.
2. A long term strategic plan should be developed to assess the objectives and needs for revision of such a program.
3. Cooperation with other licensing agencies and health care agencies should be encouraged to assist in the implementation and evaluation of the program.
4. A national resource base should be established for collecting data, including that on educational tools available.
5. The need for education of the primary care nurse in active treatment hospitals should be recognized.

F. Program for Physicians - Sara Meltzer

Continuing medical education programs for physicians are sponsored by medical schools, diabetes associations and pharmaceutical companies across Canada, including regional conferences and teleconferencing. The undergraduate curriculum in Canadian medical schools was also reviewed. It varies considerably from school to school and there is no common curriculum across Canada. Athough the curriculum for preclincial years seems to be satisfactory it is difficult to be certain of the clinical exposure of students to diabetes although most medical schools provide electives on ambulatory diabetes services. There appeared to be little emphasis on the need for a team approach to diabetes care and little emphasis on the psycho-social aspects of diabetes. There was a definite lack of any consistency or standardization from school to school.

Recommendations

1. A standard curriculum for diabetes education should be developed and made available to associate deans of undergraduate education or their equivalents in Canadian medical schools for their consideration.

2. Information should be obtained on the diabetes content of residency training programs in Family Medicine, Internal Medicine and Pediatrics.

3. The need for evaluation of the various forms of continuing medical education should be acknowledged.

G. Role of Diabetes Associations, Government and Industry - R. Gardiner

At the present time the federal government is involved in education primarily in areas related to food and nutrition. There have been some educational activities related to new glucose testing materials particularly with respect to improved standardization. Provincial governments have tended to downplay the role of diabetes education centres and most of these are now funded through global budgets in which they must compete with other activities within the hospital centre. Provincial governments have paid little attention to the education of professionals involved in these centres. Although pharmaceutical firms have withdrawn largely from the provision of written educational materials they are a major source of support for professional seminars in Canada and also provide funds for professional study for other health professionals. The major Canadian diabetes organizations provide the majority of teaching materials and information in the form of books, pamphlets etc.

Recommendations

It is recommended that:

1. The responsibilities of industry, government, and the voluntary organizations should be identified. A national meeting of these sectors may be needed to establish priorities.

2. Provincial governments should recognize the value of diabetes education centres in the effective management of diabetes mellitus. These centres should be withdrawn from global budgets and given protected line budgeting to support their establishment and efficient functioning.

H. General Recommendations

1. Model training and treatment facilities be established to provide state-of-the-art care and education to diabetic patients, and to act as regional teaching centres for training health care professionals.

2. Education research should be funded to identify behaviorally and clinically effective models of professional and patient education. This should be based on a team of investigators with expertise in clinical diabetes, educational psychology, nursing, dietetics and biostatistics.

3. A Canadian diabetes advisory board should be established to oversee and coordinate diabetes research and educational initiatives. Members should represent researchers, educators, persons with diabetes, volunteer health organizations and professional societies.

4. A national conference on diabetes education should be convened with representatives from universities and diabetes education centres and including experts in education, psychology, and other disciplines in order to improve the level of diabetes education in Canada. This conference would be responsible for establishing methods of evaluation of diabetes education and identify the cost-effectiveness of diabetes education programs in Canada. This conference should be jointly sponsored by governments and the diabetes organizations.

EDUCATIONAL ISSUES IN DIABETES MELLITUS

Steven A. Mazzuca, Ph.D. and Charles M. Clark, Jr., M.D.

Introduction

In this paper, we relate significant health policy events in the United States over the last decade that pertain to professional and patient education in diabetes mellitus. We also survey the scientific literature on the capacity of educational programs to affect chronic disease management and outcomes. We will present briefly the results of the Indiana University Diabetes Research and Training Center's Diabetes Education Study - a randomized controlled trial of physician and patient education. Finally, we will make recommendations concerning the promotion of diabetes education in Canada, based on our assessment of successes and failures of public policy initiatives, educational research and our own experience.

Health Policy Background

In 1974, the National Diabetes Research and Education Act (PL93-354) created the National Commission on Diabetes and charged the Commission to formulate a Long-Range Plan to Combat Diabetes. In its 1976 report to Congress (1), the Commission stated that with regard to education, "the knowledge, skills and attitudes of health professionals who deliver care to patients with diabetes are inadequate." The Long-Range Plan called for the establishment of Diabetes Research and Training Centers (DRTCs).

In accepting the report of the National Commission, the Congress reconstituted the Commission into the National Diabetes Advisory Board (NDAB). It authorized the Board to implement the Long-Range Plan and, among other things, to fund DRTCs in American Medical Centers. The general goals of DRTCs are to attract new investigators into the field of diabetes research and to increase the number of health care practitioners skilled in the management of diabetes and its complications. To achieve these goals, DRTCs are expected to: a) facilitate basic and clinical research; b) train postdoctoral fellows in diabetes research; c) develop and evaluate effective training programs; d) conduct continuing education programs for practising medical and allied health professionals and e) establish a model demonstration unit to facilitate the aforementioned research and training activities. There have been eight DRTCs funded for periods of three to five years since 1978. There are seven currently in operation: Albert Einstein Medical Center, University of Chicago, Indiana University, University of Michigan, Vanderbilt University, University of Virginia and Washington University (St. Louis).

The NDAB also has established model training/treatment facilities through various federal and state agencies. The Center for Disease Control, in conjunction with 20 state health departments, has funded its Diabetes Control Projects. Structurally similar to DRTC model treatment units, the state control projects emphasize health promotion to its patients and trainees. Certain groups of Native Americans have a disproportionately high prevalence of diabetes. To address this need, the U.S. Indian Health Service operates a number of model diabetes demonstration programs in the Indian Health Service. These programs also are similar to the model treatment units.

Finally, the NDAB has attempted to promote diabetes education by the promulgation of consensus standards. In 1980, a conference was convened to develop recommendations that might reduce mortality and morbidity from diabetes. The conference proceedings (2) were published in the form of a guide for primary care practitioners in the prevention and treatment of five complications: visual impairment, adverse outcomes in pregnancy, foot complications, kidney complications and ketoacidosis. On the patient education front, a set of national guidelines for patient education was circulated in 1984 (3). A certification procedure is currently under pilot testing. In all likelihood, national patient education standards and a formal recognition program will be adopted in the next several years.

In summary, the promotion of diabetes education in the U.S. over the last decade has been a multifaceted approach. Model diabetes facilities have flourished. Yet considerable effort is devoted to research and development on behaviorally and clinically effective diabetes education models. While the need for teaching and service is great, the scientific literature shows the concern about improving the effectiveness of education to be well placed.

Professional Education and Chronic Disease: Scientific Evidence

The prevalence of chronic diseases has increased dramatically over the past 20 years. As the population ages and as new advances in life-prolonging medical technology occur, the medical profession is preparing itself for an increasing number of elderly and chronically ill patients. One element of that preparation has been the development of new programs of postgraduate and continuing medical education. As mentioned earlier, national centers have been funded by the U.S. National Institutes of Health for the stated purpose of increasing the number of health care professionals skilled in the management of common chronic diseases like hypertension, arthritis and diabetes. Professional organizations also have added significantly to the volume of postgraduate and continuing medical education offerings. For example, the American Diabetes Association offered in April of 1984 a one-day workshop on the management of non-insulin-dependent diabetes mellitus (NIDDM) that was held concurrently in 24 American cities. As these sites were linked by satellite to a common national faculty, it became the largest postgraduate course of its kind in history.

The assumption behind these programs is that more competent physicians are better practitioners. In other words, physicians more knowledgeable and more skilled in the management of a given disease, in fact, translate knowledge and skill into action when it is needed. Moreover, patients who are the beneficiaries of better care are presumed to experience an improvement in the clinical course of their disease. While the necessity of a knowledge base and a repertoire of clinical skills cannot be denied, the unfortunate truth is that research on postgraduate and continuing medical education indicates that knowledge and skills are not sufficient to produce better medical practice (4-5).

Recently, R. Brian Haynes and his associates at McMaster University (4) reviewed 248 published articles and identified only seven programs which were evaluated rigorously for impact on subsequent practitioner behavior and/or patient outcome. All seven programs had a significant impact on performance; but only one of three evaluations of patient status showed a significant effect. Unlike most continuing medical education programs, each of the seven educational interventions tested had multiple components. Four programs employed audit-feedback systems to inform physicians of progress toward program goals. Other components tested successfully were criteria setting, precise guidelines or algorithms, involvement of influential physicians and increased availability of "experts".

In his comprehensive review of the literature on postgraduate and continuing medical education, Paul Sanazaro (5) asserts that competence translates into performance only under a limited number of circumstances. Successful programs tended to occur in professional environments that were conducive to high level performance. Also, improved performance was more likely to occur when there was detailed specification of practice changes that were expected as well as timely feedback regarding progress toward expected performance. Interventions directed as standard operating procedures in the care setting as well as those affecting support systems and personnel have also had a record of success. In summary, the more educational programs can influence professional and environmental factors (in addition to competence), the more likely they are to result in better care and in improved patient outcomes.

Patient Education and Chronic Disease: Scientific Evidence

There is increasing research evidence to suggest that patient education for people with a chronic disease is an essential component of effective disease management. Three comprehensive reviews of the patient education literature (6-8) converge on two general findings. First, any education is better than none. This is to say that education in any form (e.g., pamphlets, films, lectures, behavioral modification techniques) is more likely to produce improved regimen compliance and physiological outcomes than is routine chronic care without formal patient education. The second general finding is that all types of patient education programs are not equal. Two reviews (6,7) looked at the differential effectiveness of didactic and behaviorally-oriented patient education. They found behaviourally-oriented patient education to be one and one-half to three times more potent than didactic programs. The critical features of behaviorally-oriented programs were (a) emphasis on self-care rather than on disease processes and (b) mechanisms to alter the self-care environment. Some of the mechanisms tested successfully have been reminder systems, daily self-care rituals, regular contact with the same health care provider and incentives (6).

While the above findings appear to be true for patients with chronic diseases in general, we are less certain that they apply to diabetes mellitus specifically. In fact, only one true experiment in diabetes patient education was included in the aforementioned reviews. Bowen and associates (9) tested a five-part lecture/demonstration/discussion program. The program produced a modest reduction in body weight in obese patients. However, blood glucose control was not improved. More recently, Korhonen and associates (10) found no significant improvement in glycemic control resulting from an "intensive" patient education program, compared to a control group of patients receiving only printed materials. However, this study has been criticized as having inadequately conceptualized instruction. Moreover, the design of this study was such that all instruction occurred in an in-patient setting. Both intensive and traditional instructions were tested insofar as they added to glycemic control achieved through hospitalization.

To date, the scientific rationale for patient education as a part of effective diabetes care must be based on studies conducted with patients having other chronic diseases. This is the case not because well-planned diabetes patient education has been tried and found wanting. Rather, it is the case because the experimental literature on diabetes patient education is too limited to warrant conclusions.

The Diabetes Education Study

In 1978, the Diabetes Research and Training Center (DRTC) at the Indiana University School of Medicine began its Diabetes Education Study (DIABEDS) -- a randomized, controlled trial of physician and patient education in the management of diabetes mellitus. From the physician education perspective, our goal was to determine whether the salient professional and environmental factors, known in the literature of the time to be related to physician performance, could be incorporated into a postgraduate diabetes course for internal medicine residents. The goal for patient education was to combine didactic and behavioral methods into a generalized model fot diabetes patient education. The independent effects of physician and patient education were assessed on a variety of dependent variables, including metabolic control.

Subjects: Physician-subjects in DIABEDS were the 86 members of the Internal Medicine Residency Program at the Indiana University School of Medicine during the 1981-1982 academic year. Thirty-eight were interns or postgraduate level 1 residents. The remainder were in their second and third years of residency (26 and 22, respectively).

Table 1

Summary Of Baseline Assessment Of 532 Diabeds Patients

DEMOGRAPHICS	
Age Median	58.1 years
Sex (% female)	79%
Race (% black)	72%
DURATION Median	6.3 years
TREATMENT MODALITIES	
Diet alone	16%
Diet plus insulin	70%
Diet plus oral hypoglycemic agents	14%
PLASMA GLUCOSE (Mean ± S.D.)	
Fasting	217 ± 92 mg/dl
2-hour postprandial	332 ± 111 mg/dl
GLYCOSYLATED HEMOGLOBIN (Mean ± S.D.)	10.7 ± 3.1%
WEIGHT STATUS (Mean ± S.D.	
Body weight	84 ± 20 kg
Percent of ideal body weight	142 ± 31%
CONCURRENT HYPERTENSION	67%
MICROVASCULAR COMPLICATIONS	
Background retinopathy	42%
Proliferative retinopathy	8%
Proteinuria	9%
Serum creatinine (Mean ± S.D.)	1.10 ± 0.38 mg/dl
PERIPHERAL NEUROPATHY	51%

Patient-subjects in DIABEDS were recruited from the diabetic patient population in a general medicine clinic at the Indiana University Medical Center. Between August of 1978 and February 1981, 532 subjects were recruited into DIABEDS from a clinic population of approximately 1800 diabetic patients. The results of an independent DRTC assessment of this sample are presented in Table 1. Consistent with recent epidemiological profiles of diabetes, this sample was largely elderly, female and black. Ninety-five percent of the patient sample had non-insulin-dependent diabetes mellitus, as evidenced by elevated postprandial C-peptide levels. The large majority of patients were obese; yet only 16 percent were managed by diet alone. Two thirds of the sample had hypertension. Nonproliferative retinopathy and peripheral neuropathy were the most common chronic complications of diabetes, as each was observed in about half of the sample. In contrast, renal disease was relatively rare.

Clinical Setting: Patients in the Diabetes Education Study were cared for in the general medicine clinic (GMC) of a university-affiliated city/county hospital. Eighty-six internal medicine residents are assigned to staff the GMC one half-day per week with each resident responsible for the same half-day throughout his or her residency. Each resident assumes responsibility for a panel of approximately 75 patients, five to eight of whom have diabetes mellitus.

Nine weekly half-day clinics are organized into three teams of health care providers. Each team consists of three or four residents (at different postgraduate levels), a nurse practitioner, a registered nurse and a senior staff physician from the hospital department of medicine. A nearby Diet Clinic serves as a referral facility for the GMC.

This general medical facility had no individual serving in the role of a diabetes patient educator. The nursing staff dispensed written patient education materials, taught insulin injection technique and reinforced physicians' orders regarding compliance with therapeutic regimens. However, neither formal diabetes information programs, clinic-approved protocols for compliance behavior modification, nor guidelines for follow-up and reinforcement were a part of routine diabetes care in the GMC throughout the study.

Experimental Design: As mentioned earlier, three teams of residents cared for DIABEDS patients during each of the nine half-day clinics in the GMC. Therefore, the 86 residents were grouped a priori into 27 clinic teams. Six senior staff physicians and three pairs of staff members each bore attending responsibilities for three clinic teams throughout the week's schedule. Because the GMC structure and pattern of staff responsibilities could not be reconciled evenly with assignment into 4 DIABEDS groups, a randomized, incomplete blocks design was adopted. Table 2 contains a representation of assignment to groups in DIABEDS. An incomplete blocks pattern was designed so that a senior staff physician's teams would be assigned to three of the four

Table 2

Incomplete Blocks Design For Assignment Of Patients To Treatment Conditions In The Diabetes Education Study

Senior Staff Physicians	Team Assignment to Groups 1. Control	2. Patient Education	3. Physician Education	4. Physician & Patient Education
A	A_1	A_2	A_3	--
B	B_1	B_2	--	B_3
C	C_1	--	C_2	C_3
D	--	D_1	D_2	D_3
E	E_1	E_2	E_3	--
F	F_1	F_2	--	F_3
G	G_1	--	G_2	G_3
H	--	H_1	H_2	H_3
I	I_1	--	I_2	I_3
Teams	7	6	7	7
Residents	21	20	23	22
Patients	135	125	134	138

experimental groups. The "empty" group for each assignment row (rows A through I in Table 2) was varied systematically. Senior staff physicians were assigned randomly to rows. Their GMC teams and, therefore, patients receiving care from residents in those teams, were then assigned randomly to the three designated groups. In this fashion, the potential influences of senior staff, postgraduate level of residents, nursing staff, day of the week and time of the day were evenly dispersed throughout the DIABEDS design. Risk of contamination was minimized because all residents and patients for a given team were assigned to the same DIABEDS condition.

Group 1, the pure control group, was the routine education condition. Residents received instruction about diabetes only insofar as it was routinely available in the programs of this university-affiliated teaching hospital. Patients received diabetes education only as it was offered as a routine part of care in the GMC. Patients in Group 2 received a systematic program in diabetes education from staff of the DRTC, but Group 2 physicians received no special instruction. Group 3 physicians received an educational program on ambulatory diabetes management from DRTC faculty diabetologists, but their patients received only routinely-available diabetes education. Finally, in Group 4 both physicians and their patients received DRTC-initiated instruction.

DIABEDS Physician Instruction: Forty-five of the 86 internal medicine residents (14 of 27 clinic teams) were assigned to receive a multifaceted diabetes education program. The program consisted of six components. Each component was intended to address one or more hypothesized prerequisites for good diabetes care: knowledge, skills, positive attitudes, professional support and institutional support.

The first component was a handbook containing DRTC recommendations for the monitoring and management of six common diabetes problems: obesity, hyperglycemia, retinopathy, foot care, neuropathy and risk factors for cardiovascular and renal complications (11). These six problem areas were originally identified by DRTC diabetologists and by general internists and subsequently confirmed as being common in the GMC (see Table 1 for baseline assessment results).

The second component was a 6-hour course conducted by DRTC faculty for residents in Groups 3 and 4. In the course, handbooks were distributed, the recommendations reviewed, and the scientific rationale behind the recommendations presented. Course participants were afforded the opportunity to observe and practise specialized examination techniques (e.g., lower extremity examination, funduscopic examination in dilated and undilated eyes). Residents were also given access to a special 24-hour page system (component 3) through which DRTC diabetologists could be consulted concerning the appropriateness of recommendations for specific patients.

For three weeks subsequent to the course, DRTC faculty held weekly consultation conferences (component 4). Conferences occurred during the first scheduled hour of experimental team clinics. In the conferences, questions concerning specific recommendations were answered. Residents were asked whether they perceived any institutional barriers that would inhibit their following the recommendations. Any potential barriers raised were addressed by DRTC personnel (e.g., institution of an in-clinic eye dilation service). Finally, during the conferences residents were presented with a retrospective chart audit (component 5) of their panel of DIABEDS patients. Items of the audit corresponded to key recommendations. The purpose of the audit was to communicate to the residents how much (or how little) effort it would take to alter their practices to conform to the protocols in the six problem areas.

The sixth component of physician education in DIABEDS was a system of computer-generated reminders. The GMC is equipped with the Regenstrief Medical Record System (12,13). This computerized record system has the capacity to analyze patient records and to print messages to the physician in the patient's record. A computer program analyzed DIABEDS patient records and printed "reminders" consistent with key POPs recommendations during every experimental clinic in the period from August 1981 to June 1982, inclusive.

In summary, physician education in DIABEDS was a multifaceted program targeted at the knowledge, skills, attitudes and support systems related to good diabetes care. In an attempt to control for attention as a potential difference between the two groups, control physicians were given a short course in ambulatory arthritis management. The course was conducted by the Indiana University Multipurpose Arthritis Center. It was primarily didactic in nature and ran for approximately the same amount of time as the diabetes course (component 2). This "placebo" treatment did not contain specific care protocols, feedback, extraordinary consultation or computer reminders.

DIABEDS Patient Education: Patient education in DIABEDS was designed to ensure that patients would satisfy a minimal set of safety-level objectives regarding knowledge, self-management skills and compliance with diabetic regimens. A list of those objectives appears in Table 3. The safety-level objectives were selected by a multidisciplinary group of health care professionals, who evaluated an exhaustive set of objectives with respect to clinical importance and amenability to improvement through instruction. The adopted set of objectives covered seven content areas of patient education: Understanding Diabetes, Acute Complications, Antidiabetic Medication, Antihypertension Medication, Diet and Activity, Foot Care and Urine Testing.

Questions keyed to the objectives were included in the baseline assessment administered to subjects at enrollment. For patients who were to receive education (Groups 2 and 4), responses to the germane history questions were judged for appropriateness according to seven

Table 3

Safety Level Objectives For Diabeds Patient Education

UNDERSTANDING DIABETES

Defines diabetes as "too much sugar in the blood".
Describes mode(s) of control as diet, plus medication and exercise.
Wears diabetic ID at all times.

ACUTE COMPLICATIONS

Describes at least two symptoms of hypoglycemia and steps in treatment.
Carries an immediate source of CHO.
Describes at least two symptoms of hyperglycemia and at least two conditions which can result in hyperglycemia.
Verbalizes need to call health care professional if symptoms of hyperglycemia or hypoglycemia remain or worsen, and/or if ill for more than 24 hours.

DIABETIC AND HYPERTENSIVE MEDICATION

Identifies purpose of prescribed medication.
States proper time(s) and doses.
Mixes insulin thoroughly (modified insulins).
Fills syringe without contamination.
Draws up accurate dose (± 2 units).

DIET AND ACTIVITY

Uses exchange lists to solve problems of food substitution.
Selects and prepares amounts/portions of foods as recommended.

FOOT CARE

Verbalizes need to contact HCP regarding non-healing foot lesions.
States one specific result of poor foot care.
Describes procedure for foot care.

URINE TEST

Tests for glycosuria according to directions.
Tests for ketonuria according to directions.
Verbalizes need to call health care personnel if urine $3^+ - 4^+ \times 3$ with ketones.

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protocols for educational diagnosis. Each protocol covered objectives in one content area. Patients were enrolled in the appropriate module(s) of instruction depending on the educational needs diagnosed per the protocols.

Each educational module contained three elements. The first was didactic instruction in which lecture, discussion and or audiovisual materials conveyed necessary information. The DRTC instructors (i.e., nurses and dietitians) elicited comprehension periodically throughout the lesson. Also safety level skills were taught formally by means of demonstration, return demonstration and feedback. Information and skills teaching was repeated until mastery of the particular objective was demonstrated. The second element was a goal setting exercise. At the end of classroom instruction patients negotiated with their instructor the compliance goals that they felt they could attain. These goals were incorporated into a contract which was signed by both patient and instructors. Copies were retained by each. Finally, each module of instruction contained a reinforcement schedule in which the patient was contacted by phone two and six weeks after instruction. Progress towards compliance goals was assessed at each contact and reinforced where appropriate. Renegotiation of therapeutically more effective goals occurred when patients succeeded in attaining intermediate goals.

Patients, on average, received between two and three modules of instruction. Except for the Diet and Activity module, classroom contact time was about 90 minutes per module. Those patients receiving diet instruction interacted with DRTC dietitions for about 5 hours over the course of eight weeks. In addition to the patient education elements mentioned earlier, patients in diet instruction also received personalized computer-generated meal plans and menus (14) as well as a home visit. All nondietary patient education in DIABEDS occurred in the period of October 1979 to July 1981. Diet education occurred between July 1980 and February 1982.

Results: During the period of postintervention assessment, 275 DIABEDS patients (135 experimental, 140 control) agreed to submit themselves to all or part of a second series of laboratory, history and physical evaluation. The median interval between instruction and reassessment was 6.3 months for the diet module and 11.8 to 14.3 months for all other patient education modules. Every reasonable effort was made to assess the entire patient sample (e.g., payment for transportation costs, scheduling on weekends). Reasons for attrition were: death, 30 patients; physical or psychological incapacitation, 43; transfer to a senior staff physician, 32; moved from city, 13; work conflict, 24; "personal" reasons, 45; multiple failure to keep DRTC appointments, 11; lost contact by phone and mail, 58. The rate of attrition was relatively uniform in all DIABEDS groups.

In order to characterize the effects of DIABEDS education on metabolic control, we analyzed changes in fasting blood glucose (FBG), glycosylated hemoglobin (AlHgb) and body weight. Of 275 patients volunteering for all or part of post-intervention assessment, 247 allowed DRTC personnel to draw blood samples. Of these patients, 238 presented in a fasted state.

The overall F-ratio in the analysis of variance testing the equality of FBG change in the four original groups was 2.034 (df = 3,234; p = 0.110). The a priori linear contrast to test the significance of change in Groups 3 and 4 versus Groups 1 and 2 showed a significant effect for physician education (t = 1.642, df = 234, one-tailed p = 0.051). The significance of this test reflects the difference between the unweighted mean of FBG change in Groups 1 and 2 (a 4.1 mg/dl drop in FBG) and the corresponding reduction in the Groups 3 and 4 (26.1 mg/dl). Likewise, the linear contrast testing the patient education effect (Groups 2 and 4 versus Groups 1 and 2) was statistically significance (t = 1.850, df = 234, one-tailed p less than 0.05). Patients receiving education experienced an average 27.5 mg/dl drop in FBG compared to a 2.8 mg/dl average reduction among controls.

Analysis of change in AlHgb values indicated significant differences among groups (F = 3.119; df = 3,243; p = 0.024). Physician education had a significant effect on change in AlHgb (t' = 1.993, approx. df = 185.3, one-tailed p less than 0.05). The mean reduction in AlHgb among patients whose physicians received DIABEDS education was 0.39%; whereas mean change in patients of remaining physicians represented a 0.31% increase in AlHgb. Patient education also was shown to have a significant effect (t' = 2.214, approx. df = 185.3, one-tailed p less than 0.05). The mean reduction in AlHgb values for patients receiving DIABEDS instruction was 0.43%. The mean increase in "control" patients was 0.35%.

The vast majority of patient-subjects in DIABEDS were obese and non-insulin dependent. Because DIABEDS instruction for both physicians and patients stressed dietary management, body weight is included as part of the clinical picture of metabolic control. Analysis of covariance was conducted on post-intervention weight values using baseline weight as the covariate. The overall F-ratio testing equality of adjusted means was 2.439 (df = 3,240; p = 0.065). The linear contrast testing the effect of physician education indicated a statistically significant effect (t = 1.649, df = 240, one-tailed p = 0.05). The mean of covariate-adjusted body weights in Groups 3 and 4 was 83.82 kg. The corresponding value in Group 1 and 2 patients was 85.01 kg. Once more, patient education also had an independent and significant effect (1.766, df - 240, one-tailed p less than 0.05) with mean covariate-adjusted body weight of patients receiving and not receiving DRTC instruction 83.61 and 84.87 kg, respectively.

In summary, physician and patient education programs, utilizing state-of-the-art techniques of the early 1980's, had independent and additive effects on all markers of metabolic control. However, while observed differences were statistically significant, a considerable gap remained between the clinical status brought about by education and ideal patient outcomes. Norms characterizing the clinical effectiveness of physician and patient diabetes education do not exist. Nevertheless, we believe that future research will identify more potent educational models. Our experience in DIABEDS leads us to speculate about two future directions for such research.

First, we must recognize that diabetes education advocates change in behavior. Changing behavioral habits causes conflict. Education for professionals and patients alike must go beyond informing participants about behaviors that should be acquired or extinguished and attend directly to the resolution of conflicts that attempted change undoubtedly will cause. Our DIABEDS physician program attempted to address these issues by reducing the barriers to diabetes care identified by residents. Perhaps a more prospective, strategic approach to making the clinical environment more conductive to change will prove more successful than ad hoc, tactical efforts.

Secondly, patients in this study were not DRTC patients. Their primary care providers were in the general medicine clinic. Consequently, we can only speculate as to whether the same educational program conducted by primary care providers would have had the same effect. Future research on diabetes patient education should endeavor to resolve the question of whether the expertise and time for diabetes available from the specialist is a preferable substitute for the familiarity and continuity of the primary care provider for average patients.

Recommendations for Diabetes Education in Canada

As Canada embarks on this laudable effort to improve diabetes care on a national scale, we endorse the multifaceted approach to education that has characterized the American experience of the last ten years. At the root of that approach is an urgency to translate the explosion of new knowledge about diabetes treatment into practice, tempered by the realization that traditional educational models are inadequate for the task.

We recommend the establishment of model training/treatment facilities not only to serve the diabetic population directly as a source of state-of-the-art care and education, but also indirectly as regional teaching sites for trainees and practitioners. Model facilities could be located at academic medical centers, as they are in DRTCs. They can be established under the aegis of provincial health ministries, in a fashion similar to the CDC Diabetes Control Projects. Or they can service directly high-prevalance groups as do the programs of the U.S. Indian Health Service.

We also recommend the funding of educational research to identify behaviorally and clinically effective models of professional and patient education. One obvious mechanism is the independently funded research grant. In addition, for obvious reasons we are fond of the academic research and training center as an alternate mechanism. Educational research in diabetes, of which DIABEDS is undoubtedly the most ambitious example, requires a team of investigators with expertise in clinical diabetes, educational psychology, nursing, dietetics and biostatistics. It is the rare university that has an extant, multidisciplinary team to dedicate to this type of research. In contrast, the seven current DRTCs in the United States each have recruited the required expertise to develop and evaluate innovative educational models.

Finally, we recommend the establishment of a Canadian Diabetes Advisory Board. Like its American counterpart, it would be charged with the overseeing and coordination of Canada's diabetes research and education initiatives. Its membership would represent researchers, educators, persons with diabetes, volunteer health organizations and professional societies. We trust its functioning will be as successful as the NDAB - on one hand, guiding the direction of basic and clinical research and, on the other hand, encouraging the development of effective educational models to translate research findings into practice.

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DIABETES EDUCATION: PROGRAMME FOR ADULTS WITH DIABETES

Jean Tyson, R.N.

Preamble

The management of Diabetes Mellitus, ultimately under the overall control of the physician, also demands the active participation of the client. A prerequisite is that the client accepts the diagnosis. Client education is the key component to improving the quality of life for the individual with diabetes. Training, involving cognitive elements and behavioral skills (i.e. sensible eating pattern, self-medication and self-monitoring) is necessary. The better the clients' and/or patients' understanding of the essential nature of diabetes and of the therapeutic goals, the more likely they are to be motivated to follow the diabetes regimen and to take the responsibility for their disease to minimize possible complications. Thus, an educational programme is an essential part of any health care facility for chronic disease management.

A large facility is not a prerequisite in the planning of a diabetes educational programme. But an organized plan is needed to ensure that persons with diabetes are cared for excellently while they are at the facility. The programme should not only inform clients, or patients, but also should enable them to demonstrate self-care tasks and communicate verbally as to how these tasks relate to their everyday life.

Ideally, a diabetes teaching centre should establish a goal and objectives, which the programme is to reach or attain.

Goal

The goal is to enable the clients or patients and their families to initiate and maintain a day-to-day programme of self-directed diabetes management care. This management care pattern will result in fewer interruptions of a normal life style and fewer admissions to hospital by reason of complications.

Objectives

The objectives are:

1. For the newly diagnosed clients/or patients with diabetes, enabling the clients/or patients to build a sound approach to living with their condition.
2. For the clients/patients who have the condition and have problems managing it, enabling them to alter and rebuild their management programme.
3. For the clients/patients with diabetes as a secondary problem, educating them in the management of living with diabetes.

4. For health professionals, increasing their ability to understand the condition in order that they may participate effectively and knowledgeably in the educational programme.

Organization of a Teaching Facility and Programme:

A teaching centre should provide the following:

1. **Prerequisites for a programme:**

Evaluation of the clients/patients which will include medical and personal history, employment status, intelligence, knowledge of diabetes, motivation and acceptance of their disease.

Staff:

The **Clinical Director** should:

(a) be a physician with a special interest in diabetes, who takes clinical responsibility for the programme;
(b) be available for consultation when a problem arises;
(c) maintain good communications with referring physicians;
(d) be a resource person;
(e) work with the administration to achieve smooth running of the programme.

The **Diabetes Nurse Instructor** will:

(a) teach and counsel clients/patients in the centre and inpatient units by providing information about the signs, symptoms, control and management of diabetes;
(b) instruct nursing staff in in-patient units in the nursing care of diabetic patients by staff development programmes;
(c) be a clinical resource nurse, assisting staff to identify needs, planning, implementing, documenting and evaluating nursing care of the persons with diabetes.

The role of the **Dietitian** is to provide food and nutrition education:

(a) Individual diet consultation is provided for newly diagnosed persons with diabetes and their family members.
(b) Opportunity is provided for diet adjustment and review as necessary for the persons who have been living with diabetes.
(c) Instruction is given in modifying the diabetes eating plan to accommodate other dietary restrictions when necessary.

The role of the **Medical Social Worker:**

(a) To provide the team with an assessment of the patients' suitability in terms of their perception of self and perception of self in light of their diabetic condition; their support structure; stress factors in the environment and the patients/families' coping strategies, both in the present and the past. This would include a retrospective assessment of those patients presently on the programme.

(b) To provide on-going counselling service to those individuals identified by themselves and/or the diabetes team members as suffering a degree of psychosocial malfunctioning which inhibits or impairs adequate management of their diabetes condition for themselves and/or the team members. Particular focus is on the younger (17-25) type 1 diabetic.

To provide education and group counselling in the management of stress with emphasis on coping strategies and relaxation techniques. The focus is on identifying those individuals and/or groups most likely to benefit from (i.e. to implement) such education.

(c) To act with other team members in educating groups in the community. Emphasis would be on the role of stress management discussion on anxiety and depression. To act as consultant for other team members or those in the community wishing information on the above areas.

(d) To assist the team in making appropriate referrals to community social agencies and/or community programmes. This would include stress management programmes as well as volunteer agencies.

(e) To document and retain information on all aspects of psychosocial involvement in the educational programme for people with diabetes.

Supporting Services and Their Roles
(a) **Laboratory**

(b) **Occupational therapist.** Involvement includes:
1. ten to fifteen minutes lecture on why exercise is important in diabetes (see below).
2. Remainder of session involves "exercise" which is determined by the nature of the group. It may involve:
    (i) specific exercises, e.g. foot and ankle exercises
    (ii) chair exercises
    (iii)exercises (calisthenics) standing
    (iv) walking (brisk pace) in gymnasium or outside.

(c) The **Pharmacist**
The pharmacist's role is to discuss and answer questions about medications which are used to regulate blood sugar in individuals with diabetes and also about medication that may be used for other reasons, but which may affect blood sugar control or be of particular concern to the clients/patients. With type 1 diabetes (IDDM) the discussion deals with insulins, different types, different sources, differences in kinetics, issues relating to stability, storage, mixing, adverse effects and the role of insulin in the total care of

the clients/patients. With type 2 (NIDDM) the discussion deals with the oral hypoglycemic agents, differences, mechanism of action, differences from insulin, side effects, their role in relation to diet and exercise, drug interactions, etc. For both groups there follows a discussion of the use of non-prescription medications, their associated hazards and relative significance.

(d) The **Physiotherapist:** To discuss reasons for activity and/or exercise.
- (1) General muscle tone, healthfulness, sense of well-being, confidence, weight regulation.
- (2) Cardiovascular fitness. Special need is to maintain good circulation in order to prevent future problems.
- (3) Increased ventilation of lungs and therefore more oxygen for activity.
- (4) To use up stored blood sugar appropriately
- (5) Discuss briefly footwear and foot care relative to exercise.
- (6) Exercise programme (consider age, fitness level, nutritional and medical status). Outline various types of appropriate activities.
- (7) Discuss sport involvement and social aspect of same. Stress enjoyment and relaxation.

(e) **Podiatrist**

(f) **Community Health Services as required.**

A Team Approach
To have frequent meetings to ensure a consistent approach.

Psychological Aspects
Emotional support by creating a climate of mutual acceptance between individuals with diabetes and the team.

2. Contents of the Educational Programme

A checklist of the categories which can be considered essential to diabetes education:

		SUMMARY - NURSE
I	New Patients (IDDM or NIDDM)	1. Definition of diabetes 2. Urine testing 3. Insulin or oral agents 4. Capillary blood sugar - visual

SUMMARY - NURSE

II	Insulin Dependent (IDDM)	Detailed information re pathophysiology, urine testing and/or self bloodglucose monitoring, action of insulin, personal hygiene, complications, travelling with diabetes, exercise.
III	Maturity Onset (NIDDM)	1. Detailed information on oral antidiabetic drugs 2. Urine testing 3. Prevention of hypoglycemia 4. Good follow-up, exercise
IV	Self Blood Glucose Monitoring	Definition, method, glucose reflectance meters, visual strips, accuracy, value, cost, precautions
V	Insulin Infusion Pump - Education	Definition, method, type of pump, sites, failure of pump, using it correctly, mixing insulin dosage, hypoglycemia, keeping good records.
VI	Insulin - Education	Introduction, insulin antibodies, insulins available in Canada, mixing of different types, travelling with insulins

SUMMARY - NURSE

VII	Pregnancy and Diabetes	Value of excellent blood glucose control. Knowledge of the condition. Ideal weight. Accepting difficulties. Effects on the baby.

SUMMARY - DIETITIAN

I	New Patients (IDDM or NIDDM)	Group discussion on basics of eating patterns; introduction to principles of diabetes, brief discussion of individual problems and changes needed.
II	Insulin Dependent (IDDM)	Assessment of: 1. Understanding of dietary principles, 2. current eating habits 3. individual problem areas. Review of basic nutrition information. Outline objectives of diet. Explain changes which may be necessary. Give patient completed copy of G.H.E.G.
		Assessment as in II. Review of basic nutrition information.

	SUMMARY - DIETITIAN
III Maturity Onset (NIDDM)	Outline objectives of diet therapy and weight control. Patient given completed copy of G.H.E.G.
IV Diet Counselling	Assessment of current eating habits. Outline objectives of diet therapy of diabetes and explanation of changes which may be necessary. Patient given completed copy of G.H.E.G.
V Insulin Infusion Pump	Assessment as in II. Explanation of changes to be made in present eating habits.
VI Pregnancy	Evaluation of present nutritional status. Assessment and education as in II. Education and preparation for lactation and infant feeding. Ongoing assessment and education throughout pregnancy.

3. Teaching Methods

Separating the different groups of clients/patients as to age and type of diabetes. Different teaching methods suit different individuals.

Individual - Two or three sessions per week for a maximum of two months would be ideal for the newly diagnosed.

Group Teaching - Establish groups of five to eight. Group teaching promotes interaction between the individual and the team. Group teaching is to consist of formal instruction and group discussion with analysis of the perceptions and experiences of all the members of the group.

4. **Education in the Community**

Ideally the programme is to reach out to include the local diabetes association as well as the pharmacy employees, policemen, postmen, ambulance crews and the media.

Planning

The next phase for the **Ideal Model** is planning an educational programme for adults with diabetes.

1. **Selection of Teaching Personnel:** The teaching team is to be chosen for their ability to relate to others and their ability to teach.

2. **Teaching Area:** A relaxed environment, well ventilated and with comfortable chairs is required.

3. **Teaching Programme:** A planned curriculum and a time table is given in advance so that the individual will know how much time is involved. The teaching should be uniform. The ward staff should be giving the same information as is being taught in the centre.

4. **Contents of Course:** (See "Summary - Nurse" & "Summary - Dietitian").

5. **Family Participation:** One or more members of the family is to be included in the programme.

6. **Motivation:** The aim of the teaching programme is not only to inform the individual with diabetes but is to have the flexibility of incorporating suggestions from them worked into the teaching plan. This method will improve the progress of their learning.

7. **Re-instruction:** Periodic re-instruction and re-inforcement is essential.

This ideal model should not only teach but train the persons with diabetes to put their knowledge to work by practical exercises. The knowledge exercised includes:
- Diet: practice as a group at meal time.
- Urine Testing: the capacity to act upon results;
- Blood Glucose Monitoring: training to be introduced early in the teaching programme for insulin dependent people.
- Day to Day Management: capacity to modify insulin dosage without consultation.

- Hypoglycemia: recognition, treatment and prevention.
- Hyperglycemia: symptoms that indicate poor control.
- General Care and Hygiene: foot care, illness and exercise.

The programme for adults with diabetes should encompass all these factors which ultimately will leave them in charge of their own diabetes.

Present Situation

The present situation in approximately 179 Diabetes Centres and/or Clinics in Canada may be illustrated by the following range of frequency of "educational programmes" being offered:

1. Four days per week programme - 0700 to 1600 hours, where the individual and/or family come for four days of education. They are not necessarily separated into age groups or types. The practice is to take a person out of the group setting if the discussion is not applicable to the group. The Team approach is used in this programme.
2. Three days per week 0930 to 1200 hours. The patients are brought down from the wards to take part in an educational programme.
3. The teaching is done by the nurses and dietitians one day per week 0830 to 1200 hours. This is a refresher course given before discharge by the dietitian and out-patient nurse. The out-patient nurse teaches one day per week with the rest of her time being in performance of other non related duties.
4. Three days once a month 0900 to 1300 hours as needed where the newly diagnosed client/patient has to be admitted to hospital because of lack of trained personnel to conduct an educational programme.
5. Once every three months 0900 to 1700 hours, but no specified day but depending on the demand, by the dietitian, because funds are not available to provide an on-going programme.

Conclusion

All the frequency examples cited above do not conform to the Ideal Model but should be made to fit if administratively reorganized.

Recommendations

All hospitals provide an educational programme with family participation and follow-up appointments as necessary.

Evaluation of the educational programme in terms of client/patient knowledge, client/patient action and effect on diabetes control which is to be built in to the programme at its inception.

Post-Graduate courses for the Health Professional in all disciplines is to be encouraged.

Education by TV Satellite or other networks such as the Knowledge network so that knowledge can be given to those in remote regions.

A standardized Diabetes Teaching Programme across Canada is to be encouraged so that the quality of diabetes care would be improved and be of a consistent standard across Canada.

Summary

Outlined is an approach for an ideal situation for a diabetes education programme for adults, recognizing that it has to be flexibile to meet the needs of any given area. It is recognized also that difficulties may be encountered such as the inflexible attitude of people in various professions who wish to keep clients/patients "captive" for their own practice and not recognize the value of the knowledge or contributions which may be offered by other disciplines.

If the Canadian Health Care System were to develop and implement a standardized Diabetes Teaching programme, there would be continuity in the quality of diabetes care from province to province and/or to the territories.

Increased training and education for both professionals and clients/patients are to be encouraged.

Social interchange amongst patients/clients is to be encouraged so that the patients/clients will acquire more knowledge about their condition and so that, in the case where there is some reticence in accepting their condition, such reticence may be overcome.

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EDUCATIONAL APPROACH AND PROBLEMS RELATING TO CHILDREN WITH DIABETES AND THEIR PARENTS

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Introduction and Objectives

Certain factors are specific to the pediatric and adolescent age groups. Unlike the adult situation, one is dealing with several interested parties, the parents, the patient and the siblings. Extended family, the school, babysitters, sports leaders, also come into play. Depending on the age of the child, some may be more or less involved, but parents are pivotal until later adolescence. The idea is often expressed that the young child should become autonomous and answer early and singly to the doctor, thus leaving out the parent in order to avoid a presumably deleterious triangle that is purported to be the cause of the adolescent rebellion. In my mind, this is not only false but dangerous. The adolescent needs the support and supervision of his parents, and thrives under it when it is given in a positive fashion. However, blame and quarrelsomeness are self defeating.

Many psychological factors come into play at the onset of diabetes. New parents are shocked by the diagnosis, saddened and often show anger, denial and depression. In time, acquiescence, if not always acceptance, follows. The parent's attitudes, however, are very important in defining his own. Obviously, existing family and social problems greatly influence the adaptive process. The diabetic child rarely overtly reacts at the onset of his disease. Early denial is often passive and manifested as a lack of interest in the teaching process. Open rebellion tends to be delayed sometimes for years after the onset of diabetes and often appears at adolescence, but can occur at any time, even from the very beginning. Children occasionally assume a brave and protective attitude towards their parents in the face of depression or incapacity on their part to acquire the necessary knowledge, either because of language or other difficulty.

The initial approach to the family should be realistic. In an effort to be encouraging, health professionals sometimes are tempted to paint an overly rosy picture of what life with diabetes is all about, using phrases such as "your child's life will be entirely normal". Reality is that life ahead will have to be changed somewhat to accommodate diabetes and it is best to say so from the beginning. This does not exclude a due emphasis on positive factors such as the fact that insulin is life saving and that with good control, one can anticipate good health and adequate energy to carry out a full life with normal expectations of achievement. One should remember to bring to their attention as well the tremendous strides we have seen in diabetic research in the past few years as well as the exciting possibilities lying ahead. One should certainly point out the dangers. Diabetes is a lethal disease, if one discontinues insulin. With inadequate control, late complications can occur as early as ten or fifteen years after the onset of the disease and pregnancy without good control is fraught with danger for both the mother and her unborn child.

The Ideal Situation

The actual teaching of diabetes is adjusted to the age of the patient. For the under-school age child it will be directed almost exclusively to the parents, who in turn will teach simple basics to the child. By 6 to 12 years of age, a child can participate in practical teaching on the basics of diet, hypoglycemia, testing, the meaning of blood sugar and the administration of insulin. From the early teens onwards, the patient should participate fully in the teaching process with his family. He should be encouraged to gradually assume responsibility for his diabetes with the understanding that he still needs a lot of parental support and supervision. One aims for full autonomy by the late teens. This is also the best time to introduce to the diabetic himself the concept that control influences the development and severity of late complications and the outcome of pregnancy. These facts should be discussed from the beginning with parents, but are of little relevance to the young teenager or child who is much more concerned with satisfying the desires of the moment. Discussing complications with children and young adolescents only serves to produce anxiety and sometimes anger and rebellion.

What is the ideal teaching facility in the pediatric age group? Laron ($_1$) Golden ($_2$), and others have shown that a hospital or clinic-based team comprising physician(s), nurse(s), dietitian(s) and social worker(s) with a psychological/psychiatric backup is a basic requirement. They add to this the necessity for 24 hour, 7 day a week availability by telephone after discharge. In our experience, initial teaching requires a minimum of 4 hours each from the physician, the nurse and the dietitian and this teaching is usually given over a period of 7 to 10 days. In most centers, the patient is admitted to hospital, but where good day care facilities exist and where the metabolic condition of the patient permits, much of the teaching, if not all, could be given on an outpatient basis. There are, however, some advantages to hospitalization such as availability of overnight blood sugar monitoring to ensure that nocturnal insulin action is not excessive. Objectification of the seriousness of the diabetic condition in the eyes of child and parent is also easier to achieve when an admission takes place. At the end of the teaching period, the family's ability to cope with diabetes should be checked through the use of a questionnaire. In centers which undertake the long term care of diabetic patients, further teaching occurs on an ad-hoc basis at the time of follow-up clinic visits and telephone contact for intercurrent illness.

Diabetic camping can and should be an important adjunct to teaching of children particularly those who were too young to receive it in hospital at the onset of their disease. This is not always the case however, as the general camp program has a tendency to preempt the medical component. Ideally, refresher courses should also be available on a regular basis for parents and patients. Local diabetic associations in conjunction with pediatric diabetic centers in certain localities presently provide this to a small extent but participation is difficult to predict and is at times poor. Why? Lack of motivation to practise good diabetic control is a major problem which we have perhaps not sufficiently addressed. New behavior modification techniques should undoubtedly be tried, but would require additional professional staff for the diabetic team. It is a fact that recent advances in management techniques of diabetes are not meeting with the expected results largely because of parent/patient non-compliance.

Actual Situation In Canada At Present

The incidence of diabetes in Greater Montreal has been established over the last ten years to be of the order of 10/100,000 in the age group under 17(4,5,7). This conforms to the experience reported by others in Canada and the United States(3,6). In most large Canadian cities, particularly in University Centers one finds pediatric diabetic teams of the type described above. Table 1 presents the results of an incomplete telephone survey of the main pediatric diabetic teaching and treatment centres in Canada. Table 2 gives a breakdown of the clinical and teaching activities of the diabetic clinic at the Montreal Childrens Hospital over the period 1982-85.

Pediatric diabetic clinics tend to gather to themselves an important proportion of the local diabetic pediatric population and to attract a certain number of consultations from the periphery. There remains, however, a large number of children from small non-university communities and even from large cities who are not referred at the onset of their diabetes to a diabetic teaching center. The information imparted to them tends to be scanty and of questionable quality, as the physician delivering the care may himself have little experience with the condition and little or no access to specialized dietetic and nursing help(2). Since the first few years of insulin-dependent diabetes (IDDM) are often marked by relative ease of control due to the continuing secretion of some endogenous insulin, the physician and patient are often lulled into a sense of false security and do not recognize the need for specialized help. In time, the diabetes becomes more difficult to control, and the doctor, the patient himself or his parents may approach the diabetic center. By then poor habits of care have become established, and it is a frequent experience that the more demanding regimen proposed is rejected until the appearance of late complications of diabetes makes it mandatory. By then the horse is out of the barn and less benefit will ensue from improved control.

Table 1

SURVEY OF A FEW CENTERS IN CANADA FOR THE TREATMENT AND TEACHING OF DIABETES TYPE I IN THE PEDIATRIC AGE GROUP (under 18 yrs)

LOCATION	CLINIC PT LOAD/ AREA POOL	NEW PATIENTS PER YEAR	TEACHING		CLINIC STAFF				OUTREACH PROGRAM	OTHER
			IND	GROUP	MD	RN	S.W.	Ddt		
Vancouver Children's Hosp. (Dr. J. Tze) under 18 years	$\frac{500}{1000}$	50	x	x	2+	2	1 PT	2	yes	Refresher courses
Calgary Children's Hosp. (Dr. R. McArthur) under 18 years	370	60	x		2	1	1	1	yes	Refresher courses
Winnipeg (Dr. Heather Dean)	$\frac{150}{500}$	25	x		1	1	1	1	New Prov. funded services outside hospital as part of global DM program.	Refresher. Previous DM clinic at children's hospital disbanded.
Toronto Hospital for Sick Children (Dr. R. Ehrlich)	$\frac{800}{?}$	100 Gr. Toronto Incidence 10/100,000	x	x	3	2	1	2	Wide referral area.	Many patients cared for by LMD + clinical consultation yearly.
Montreal Children's Hospital (Dr. M.M. Belmonte) under 18-21 years	$\frac{350}{?}$	30-40 Incidence Dr. Montreal 10/100,000	x	x	1 FT 3 PT	1	1 PT	1 PT	Wide area for consultation and follow-up	See attached clinic statistics. Table 2
Ste-Justine Hosp. (Dr. R. Poirier)	$\frac{380}{?}$	40-50	x		3	1 PT	-	2	Wide area for consultation and follow-up.	
Halifax Children's Hospital (Is. Walton Killam) (Dr. Bruce Morton Pediatrician)	$\frac{100}{200+}$	25-30	x		1	1	1	2 PT	Yes	Day care service under Dept. of Endocrinology
St. John's, Nfld (Janeway Children's Hospital) (Dr. A.J. Davis) under 16 years	$\frac{160}{200}$	20-25 Incidence in Nfld 13/100,000	x	x	3	1	1	2	Province wide via telecommunication, consultation and visits.	

- All have access to diabetic camping

- None are conducting prospective studies to evaluate efficacy of their teaching procedures

Table 2
MONTREAL CHILDREN'S HOSPITAL DIABETIC CLINIC - YEARLY STATISTICS

	1980-81	1981-82	1982-83	1983-1984	1984-185
	Mean/Total	Mean/Total	Mean/Total	Mean/Total	Mean/Total
Total Patient Load	392	387	386	370	369
Newly Diagnosed (M.C.H.)	47	37	28	41	39
Transferred to M.C.H. (old)	11	13	11	14	13
Total New Patients to M.C.H.	58	50	39	55	52
Transfer to Adult Care	22	29	21	57	31
Transfer to Elsewhere	16	19	14	15	22
Total No. of Admissions	166	197	185	200	175
Ketoacidosis (new)	4	5	3	8	7
Ketoacidosis (old)	6	4	11	6	6
Non Coma (new)	54	32	20	33	32
Hypoglycemia (O.U. and Wd.)	10	25	(12 + 10)	(11 + 11)	(7 + 5)
GI Upset ± Hypogl. (O.U. and Wd.)	8	12	15	(17 + 11)	(18 + 2)
For Control of DM	38	52	54	55	42
For Surgery	22	22	18	16	12
Psychosocial (reg. Wd.)	12	9	8	13	15
Psychiatric (7D + Adol. Day)	3	3	(1 + 1)	(1 + 0)	(1 + 0)
Other -	9	33	pump 3 + 29	pump 6 + 22	2 + 26
Total Hospital Days	2353	2453	1754	2029	1736
New DM - Total	664	381	254	505	537
Average Stay	11.4	10.2	13	12.3	13.6
Psychosocial (Psychiatric 7-D)	146 (596)	300 + (419)	94 (365)	215 (365)	261 (365)
Average Stay	12.1(198.6)	33 + (139)	12 (365)	16.5 (365)	16 (365)
Other - Total	947	1352	914	944	1158
Average Stay	10.1	9.13	6	6.5	9.9
No. of Pts. Who Received Teaching	310	279+	250+	210+	208
In-Patients	160	129	150+	110	133
Out-Patients and Visitors	150	150+	100+	100+	75
Clinic Visits	1255	1731	1610	1423	1327
Total Scheduled	1407	1437	1313	1319	1359
D.N.A.S.	383	412	332	355	336
Actual Clinic Visits	1024	1025	981	964	1023
Office (inter-clinic) visits	231	706	629	459	304
Telephone Calls (per day)	20+ day	20-25	20-25	20-25	20-25
No. Who Attended Camp	71	67	69	64	58
Deaths (detail)	0	0	0	0	2-CF & Thal.
Home Visits	0	0	0	0	3
Social Service Referrals	82	65	68	59	67

A better scenario is that of the adult endocrinologist taking care of a certain number of juvenile diabetic patients alongside the adult population. This is not entirely satisfactory, however, because the adult milieu and its lack of focus on pediatric problems, particularly the psychosocial, leave out a very important component of both teaching and care. Alternatively, the local pediatrician may "hold on" to his diabetic patients. He/she is certainly well prepared to deal with chronic disease in children but may not have enough diabetic patients to allow acquisition of the expertise needed to deal with the complex issues of the disease. The pediatrician often sins by being too psychologically oriented and insufficiently aware of the newer evidence linking quality of diabetic control to the late complications of the disease. As a consequence he/she frequently tolerates a rather "loose" regimen of control in the misguided belief that the patient will be spared psychological trauma(8). Furthermore, the solo pediatrician seldom has access to diabetic nursing and dietetic teaching, nor can he/she usually assure the necessary 24 hour/day, 7 day a week availability required by his/her patient after discharge from hospital.

Conclusions

The situation in Canada with regards to young (under 18) diabetic patients has improved greatly in the past 10-15 years. A number of diabetic clinics staffed in a way similar to that described by Laron (1) and Golden (2) have been established in most provinces of Canada (Table 1). They tend to be attached to a university pediatric unit and to serve a large porportion of the surrounding population in an on-going fashion and to provide consultation to small numbers of patients from the periphery. There remains, however, a sizeable number of pediatric diabetics with little access to satisfactory teaching and follow-up both in remote areas and in non-university urban centers.

Recommendations

In view of the immediate and late complications of poor diabetic control in children and young persons (9) and the cost thereof to society in the short and long term, efforts should be made to provide first class teaching and follow-up to these patients from the time of diagnosis. Where a community can group 100 or more young diabetics, a "teaching and care" team should be set up in the hospital best suited to support it and so constitute a diabetic teaching and care center both for the immediate community and the periphery. This should be headed up or at least have participation by physicians with diabetic and pediatric expertise. Dietetic, nursing and social service staff should also be available along with psychiatric consultation. Children from remote areas should be given access to diabetic care centers through provision of travel and lodging expenses for the child and parent(s). Physicians should also be urged to seek these services for their patients preferably at or very soon after diagnosis. Special government funding would undoubtedly be required.

Better funding of large diabetic care centers in university hospitals would afford the possibility to study behaviour modification programs. It would also allow more staff for continuing education of families.

Diabetic camping should be encouraged and supported. Accessibility to young diabetics from remote areas should be assured through travel and bursary funding. However, camps have also the duty to provide an adequate medical and educational input.

The effectiveness of teaching and treatment programs should be evaluated in a prospective fashion. In the short term end points could be the glycosylated hemoglobin (8) and quality of life. In the long term one would need to look at the occurrence of diabetic complications as well as productivity, quality of life, and reproductive capacity. Such a study requires that internists and "adult" diabetologists assume an interest in making such long term evaluation possible. A close liaison between pediatric and adult care is also desirable to facilitate the passage from one to the other at the end of adolescence. Without this link many young adult diabetics flounder without stable medical attention until the appearance of late complications, when it is too late.

SUMMARY ABSTRACT

Pediatric diabetics present educational needs peculiar to the severity of their disease, the potential for late complications and the factors surrounding the fact that one is dealing with growing children whose future lives depend on maintenance of good physical and emotional health. The necessity to work through parents and other advocatory groups further complicates the task. Suitably staffed clinics are required to provide the teaching and care required. Travelling funds are needed to make these units available to patients living at a distance. Undoubtedly, the funds expended to realize a universal program for young diabetics in Canada would be far less than the cost to society today resulting from the early mortality, morbidity, failure to be gainfully employed, and obstetrical hazards seen in many type 1 diabetics.

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NUTRITION EDUCATION FOR PEOPLE WITH DIABETES

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Introduction

A regulated food intake is essential in the management of all types of diabetes. (1) It depends upon diet counselling and nutrition education, two distinct but related processes in diabetes management.

Diet counselling is the process of developing a diet prescription. It requires the dietitian nutritionist to work with the person with diabetes and family members to develop one or more meal plans, tailoring the diet prescription to meet the unique needs of the individual. Diet counselling must be provided on an individual basis, taking into account the following factors:

- Type of diabetes - a determinant of general diet strategy;
- Treatment modalities augmenting diet - insulin (types, dosage schedule, pattern(s) of release), oral hypoglycemic agents (type, pattern of action), exercise (pattern and degree of activity);
- Work schedule and availability of food on the job or at school;
- Variations in schedule - weekend vs weekdays, seasonal work;
- Ethnic background - health beliefs, food beliefs, food habits and preparation;
- Composition of foods included in the meal plan;
- Economic limitations;
- Willingness of family and friends to support changes in food habits;
- Willingness of individual to change eating habits;
- Use and social importance of food and alcohol;
- Normal nutritional needs for age;
- Weight for height and frame; and
- Special considerations, e.g. growth, pregnancy, weight loss, athletic training.

Diet counselling relates specifically to the prescribed treatment of diabetes and requires the expertise of a professional dietitian nutritionist. Effective diet counselling involves the dietitian and person with diabetes in a partnership to determine personal attitudes and beliefs about health and food, to understand the person's values and priorities, to assess the person's readiness to change routines and lifestyle, to set realistic goals and to develop a commitment to work toward these goals.

Nutrition education is distinct from diet counselling. It is the transfer of information, with instruction in meal planning skills and opportunities to practise. Education offers realistic problem solving exercises with time for questions to clarify whether the teaching has been understood. Throughout the process, the diabetes educator must assess whether learning has taken place before moving on to the next step. Opportunities for frequent review and follow-up are an essential part of the educational process.

Nutrition education begins during diet counselling and continues either on an individual basis or in groups. The diabetes educator who provides nutrition education is a professional dietitian nutritionist. Reinforcement of learning is necessary and can be provided by a nurse with a special interest in, and the knowledge of, diabetes. Nutrition education of people with diabetes requires the diabetes educator to:

- Instruct the individual (or parents) and family members, particularly those responsible for meal planning and food preparation;
- Explain the relationships between food intake and diabetes control (blood glucose and serum lipid levels) and good health;
- Classify foods into a system of food groups and explain how these relate to the meal plan;
- Explain the importance of food quantity in diabetes control;
- Distinguish between food categories and relative effects of foods on health in general and diabetes in particular (blood glucose, serum lipids and body weight);
- Explain the interchangeability of food portions within a food group;
- Demonstrate how to use the prescribed meal plan with food groups to achieve consistency of macronutrient intake while permitting variety in food selection;
- Expand the variety of food choices through the use of auxiliary educational tools, e.g. cookbooks, lists of commercial foods, nutrition labelling;
- Discuss how to cope with diet during illness, travel, shift work, meals away from home, parties, delayed meals, traditional holidays, sporadic exercise;
- Explain the use of food to prevent/treat hypoglycemic reactions; and
- Plan for follow-up visits with the dietitian nutritionist to review and revise the prescribed meal plan as necessary to ensure continued appropriateness.

Diet counselling and nutrition education are closely related since the latter is required to implement the former. Both together are an integral part of ambulatory diabetes care.

THE IDEAL STATE

Education of People with Diabetes

Successful diabetes management depends upon people with diabetes and their families having been well informed and trained in diabetes care by knowledgeable health professionals. Both diabetes educators and people with diabetes must know what to do and why the action is important to diabetes management. Those with diabetes or their family members make a multitude of daily decisions related to diabetes control. They must be able to function in their daily activities as normally as possible and know when to contact their health care providers for assistance. Accessibility of health professionals is crucial to support a system of ambulatory diabetes care based on self-management.

Since diet is essential in the treatment of all types of diabetes, all people with diabetes, estimated to be over one million in Canada, require upon diagnosis accessibility to both diet counselling by a professional dietitian nutritionist and nutrition education by a knowledgeable diabetes educator. Assessment, teaching/learning, evaluation and opportunities for follow-up are important parts of diabetes education. (2)

Diabetes education has recently been shown to significantly reduce hospital admissions for diabetes related problems. (3) Accessibility to diabetes education is therefore a key to successful ambulatory care of diabetes and reduction of emergency admissions to hospital. (4)

Ideally, there would be a uniformity of information in diabetes education throughout Canada. In the highly mobile Canadian society, people will probably be in contact with health care providers in different parts of the country. When people with diabetes and their families turn to health care professionals for advice in diabetes self-management, their confidence is enhanced and their learning process reinforced through consistency in both the factual information given and the principles advocated. Mixed messages are confusing and may do harm if the confusion leads to inappropriate self-care. Use of the same or coordinated teaching tools by various diabetes educators across the country can help to alleviate the problem of mixed messages.

Similar principles of nutrition serve as the basis of dietary recommendations accepted by the diabetes associations of many countries.(1,5,6,7,8) Different dietary tools have been developed in each country to implement the recommendations. To the diabetes educator these different approaches have the same principles in common, however to the person with diabetes the teaching tools of diet seem quite different. It is confusing enough to have different countries using different teaching tools; when this happens within a country or within a city, it is very difficult for the person with diabetes who changes location.

Equally important in preventing undue confusion is a consistency in approach - avoidance of mixed messages - by different members of the health care team. Hearing the same message from different health care providers using different words and examples, each with a slightly different emphasis, can help reinforce learning. However, if the message is conflicting or conveys a totally different emphasis, confusion results. The person with diabetes does not know what or whom to believe. Control of diabetes may suffer as a result of indecision or inappropriate decision making. Close communication among members of the health care team and a common understanding of the principles of diabetes management among the various disciplines can help to alleviate this problem.

Continuing education programs for health professionals would provide a common basis of knowledge and also foster a mutual respect for the more specialized expertise of the other members of the diabetes education team. The problem of mixed messages can be avoided through referral by one member of the team to another who is better prepared to answer the question in depth and instruct in the area of their particular expertise. There is a great deal of interchangeability of knowledge and sometimes of roles among members of a compatible diabetes education team. Such compatibility is highly desirable. It develops from individual competency and mutual respect.

For the sake of continuity in diabetes education in general, and the nutrition education component in particular, it is important that the different teaching professionals be familiar with the principles of a nutritional care plan for the particular type of diabetes and with the food system which the individual with diabetes has learned. The Canadian Diabetes Association has published nutritional guidelines which set forth the goals of diet therapy, general dietary recommendations, specific dietary strategies according to the type of diabetes, and practical considerations involved in implementing a diet prescription. (1,5) A variety of nutrition education materials have also been produced to provide a uniformity and continuity of information across Canada.

Diabetes education must be tailored to meet the needs of the learner for several reasons. First is the issue of readiness to learn. The diagnosis of diabetes is an emotional shock which often reduces the individual's readiness or ability to learn. (9) Even after recovery from the initial shock, other stages in the acceptance of chronic disease - anger, denial, depression - may create periods of learning inhibition, interspersed with periods of readiness. A message given during a period of inhibition will not be received, while lack of information during a period of readiness can lead to frustration by those with diabetes and their families. Learning about diabetes and self-care is a long process which cannot be accomplished during one visit with a health professional or one hospitalization. Thus the need for continued follow-up is paramount.

Secondly, people learn in different ways. (10,11) Some people need to see the whole before they can understand its parts, whereas others need to learn about the parts before understanding the whole. Diabetes educators who are able to recognize and accommodate these different learning styles will more effectively assist the people with diabetes and their families whom they teach. In addition, some people are readers, while others prefer to learn by listening. Many people need examples in order to grasp a general concept; they may also need a period of practice at home before understanding completely. Thus, diabetes education may begin during hospitalization, but must continue over a period of time on an out-patient basis.

Thirdly, learner-oriented education is the most effective. (12) It encourages people to become involved in problem solving related to themselves, so that what is learned is relevant and applicable. Learner-oriented education is conducted in a relaxed, non-judgemental atmosphere in pleasant surroundings and is enjoyable.

Finally, learning about diabetes is enhanced in centres where education is combined with treatment. Individuals can see the effects in themselves as treatment changes. This lends credibility to the education and develops or strengthens the individual's belief that treatment matters. Such recognition may lead to a greater willingness to accept responsibility for diabetes self-care.

The fact that people have different learning styles means that the diabetes educator requires a variety of teaching tools and methods to meet the learning needs of people with diabetes. Information must be presented when the learner is ready and receptive, usually in a step-wise progression according to their readiness and learning style. Teaching tools which present information in modules allow both the diabetes educator and the learner with diabetes to select information which is relevant at the right time.

The diabetes meal plan is the basic treatment plan, necessary in all types of diabetes and developed through diet counselling. The person with diabetes and his or her family are charged with the responsibility of implementing the plan daily under a variety of circumstances. Successful implementation of the meal plan depends upon nutrition education in which the individual and family members have the opportunity to learn how to translate the treatment plan into meals using appropriate foods.

Ideally, the meal plan will offer sufficient variety to avoid becoming monotonous. It offers the maximum variety when presented in a general way, the specific foods being chosen by the individual from a set of acceptable alternates, e.g. food groups.

A food classification system, suitable for use in the treatment of all types of diabetes and based on the nutritional guidelines (1,5), would meet the following criteria:

1. Provide the nutrients normally required for health;
2. Allow a controlled energy intake;
3. Provide for consistency in the type and amount of carbohydrate eaten; and
4. Promote a reduction in fat intake.

The resulting food group system would be considered the basic teaching/learning dietary tool. It requires the support of related materials to expand the variety of food choices, making the meal plan more adaptable to daily living. Examples of such materials are commercial food lists, classified according to the basic food group system; cookbooks, with recipes related to the system; and specialized information related to dietetic foods, special occasions, dining out, alcohol, travelling, exercise, illness, pregnancy, youth, elderly.

Nutrition labelling of foods offers a potential benefit to people with diabetes as it could greatly expand the variety of foods which may be eaten safely. Interpretation of food labels is a part of nutrition education for people with diabetes. It will become all the more relevant when a majority of foods carry the information to allow consumers with diabetes to decide whether to eat the food, how much would be safe to eat, and how the food would fit into their diabetes meal plan.

In Canada's multicultural society there is an important need for diabetes education materials in many different languages. Linguistic translations are helpful but not sufficient. Cultural translations of dietary information are necessary in view of the strong association of culture with food. (13) A cultural translation of the food group system would classify traditional foods of the culture into the appropriate groups as well as being a linguistic translation of the whole. Ideally, the format would be consistent to enable the diabetes educator to recognize the information in the unfamiliar language. Either that, or the cultural translation must be presented in a dual language format, e.g. Chinese/English or Chinese/French.

An added difficulty exists in diabetes education, namely that some people who require the education may be ready to learn, but unable to read any language, including their mother tongue. Obviously, translations are not the answer in such cases. The diabetes educator will first have to determine whether the person reads and, if not, be assured that there is someone available to assist the individual in the use of handout materials. The basic dietary tool therefore, must be available in a form which addresses the needs of people who are unable to read.

Visual impairment is also common among the diabetic population and diabetes is the leading cause of new cases of blindness. (14,15) Educational materials must be developed keeping in mind the need for large print and sharp contrast between the printed word and background.

Thus, there is a need for a variety of tools to meet the learning needs of a varied population. Dietary tools must be available to enable the educator to present information at basic and advanced (or expanded) levels to a multicultural population with varied reading abilities and visual limitations.

Education of Health Professionals

Professional education is another important consideration in the nutrition education of people with diabetes. Teaching tools cannot stand alone. To be effective the tools require explanation by knowledgeable health care providers, all expressing the same principles with consistent messages.

The dietitian is the member of the health care team who has a detailed knowledge of food composition, meal planning, food preparation and the physiological effects of the food. The dietitian also brings to the diabetes team an understanding of the cultural and economic implications of food in the family.

Continuing education is vital to keep the dietitian informed of advances in nutrition research as they relate to the dietary component of diabetes treatment and education. Time is required for the dietitian to attend continuing education programs and seminars to upgrade knowledge. Dietitians, in turn, have a responsibility to keep their colleagues of the diabetes team informed. They also have the responsibility to learn from team members and continuing education programs about the non-dietary aspects of diabetes treatment to understand the interrelationships among the treatment modalities - diet, insulin or oral hypoglycemic agents, and exercise. (16)

All members of the diabetes team need education and continuing education to prepare them to assist a multicultural population. Such education would include an awareness of health beliefs, traditional food habits and methods of food preparation. (17) Knowledge of and respect for the individual's traditional or preferred style of communication (e.g. direct, indirect) assists the health professional in being a more effective diabetes educator. (18)

THE CURRENT STATE IN CANADA

Evolution of the Food Exchange System

From 1956 to 1979 the majority of dietitians used the booklet "Exchange Lists for Meal Planning for Diabetics in Canada", developed and published by the Canadian Diabetes Association (CDA). It was revised five times in its 23 years of use. In 1956 some Canadian hospitals used the new food exchange system of the American Diabetes Association (ADA), but most had developed their own. Thus, nutrition education of people with diabetes was very fragmented leading to confusion, not only among patients and families, but also among the dietitians, nurses and physicians teaching them. The CDA, chartered in 1953, set as one of its priorities the development of a food exchange system which would bring a unified approach to the diet prescription and dietary education of people with diabetes in Canada.

Throughout the twenty-three years from 1953 an increasing number of hospitals used the CDA system, but some, principally those in Québec, continued to use the ADA system, and Manitoba adopted the system developed by the St. Paul Children's Hospital (Minneapolis-St. Paul, Minnesota). The efforts of the CDA to bring a unified dietary system were more successful in the other provinces although not entirely even by 1979.

Dietitians who used the CDA system (and the ADA, for that matter) found it was too complex for many individuals and their families, a principal reason Manitoba had adopted the simplified St. Paul's system. Informal contact by the staff dietitian of CDA with her colleagues across Canada indicated that most dietitians had developed their own simplified form of the CDA food exchange system to teach those individuals who could not understand the booklet. These materials ranged from handwritten meal plans, to simplified food lists, to picture books with handmade drawings or pictures of foods cut out of magazines. Some had colour coding of the food groups for ease in identification.

The CDA responded to the expressed need for a simplification of the food exchange lists with the decision in 1975 to investigate the simplification and revision of its exchange system and materials. By 1976 a National Diet Simplification Task Force had been set up by the Canadian Diabetes Association with one dietitian active in diabetes education from each province appointed by the provincial dietetic association, and liaison dietitians from the Canadian Dietetic Association and the Professional Health Workers Section of the Canadian Diabetes Association. A non-dietitian was appointed by the Department of Indian and Northern Affairs to represent native people at the request of CDA.

At the first meeting of the Task Force in 1976, dietitians expressed the need to develop a basic dietary tool to teach people who require a simplified approach, are not page turners and consequently do not learn well from books, or do not read any language. It quickly became clear that to address the learning needs of such individuals all the information necessary to plan a day's meals must be on a single (large) sheet with drawings of foods in sufficient numbers to prevent boredom and allow for a considerable range of food preferences on a national and multi-cultural basis. The Task Force recognized that while a simplified tool must meet the therapeutic needs of all types of diabetes, the majority of its users would be adults with type II diabetes.

The impact of the Canadian government's decision to convert to the Systême International (metric measures) was considered along with the following needs:

- to provide learners and diabetes educators with a choice of formats designed for different learning styles and levels of comprehension;

- to develop a visual format to teach non-readers, adaptable to the eating habits of a variety of cultural groups;
- to revise, update and metricate the CDA exchange lists booklet for those desiring more detail;
- to encourage uniformity of information through wide-spread use of CDA materials by making them as attractive as financially possible;
- to use Canada's Food Guide as the basis of the nutritional care system;
- to reduce the stigma of having diabetes by omitting the word "diabetes" from the title;
- to encourage the family to have the same meals as the person with diabetes, providing important psychological support;
- to promote progressive learning by providing the basic tool in different formats and support materials consistent with the basic tool(s), which could be introduced according to learning readiness;
- to employ a modular approach in the basic dietary tool(s) which would permit expansion of specific topics using support materials, e.g. pamphlets, cookbooks, flip charts, games, audio-visual aids.

The volunteer Task Force, funded by CDA, met semi-annually for four years from 1976 to 1980. The Core Working Committee, which included the Quebec representative, met more frequently to develop the "Good Health Eating Guide" (GHEG) by the Canadian Diabetes Association.

During Phase I, the Task Force collected and examined over one hundred simplified dietary tools in use by dietitians throughout Canada and in other countries. All of the existing tools were a variation of an exchange system, but none met the criteria as set forth by the Task Force (listed above). Therefore, the National Nutrition Committee of CDA decided to proceed with Phase II of the Task Force - to develop a suitable simplified system followed by a revision of the existing CDA exchange system, making it consistent with the simplified system and the current concepts in nutrition and diabetes.

The first step of Phase II was the development and testing of a poster form of the GHEG. The production and field testing of a prototype was funded by a grant from the Health Promotions Branch, Health and Welfare Canada. The testing was conducted by CDA volunteers, coordinated by the CDA National Office staff dietitian, assisted by the Health Care Research Unit, Department of Community Medicine, University of Toronto.

Based on the test results of over one hundred dietitians and nearly six hundred people with diabetes from all provinces, the GHEG poster was modified as described elsewhere. (19) Evaluations were also solicited informally from specialists in adult education at the Ontario Institute for Studies in Education. Their advice to build different learning cues into the poster was implemented through the use of different colours, symbols and positions of the food groups. These cues were repeated in the meal plan.

In 1977, Statistics Canada advised the CDA that twenty-nine percent of the Canadian population were functionally illiterate. In response to this finding the Task Force made efforts to develop the GHEG poster to be suitable for use with non-readers and paid special attention to the test results of those who were unable to answer a question specifically designed to test reading ability.

The test results indicated that 68 percent of the readers were able to correctly plan a meal using the poster as compared with 21 percent of the non-readers. When the readers and non-readers were combined, 65 percent of the total population sampled were able to perform the most important functional task in following a diet.

The test protocol allowed individuals only ten minutes to look at the poster before being expected to answer questions about it, including what foods and how much they would eat for their noon meal correctly using the sample meal plan written on the poster. The testers, mostly dietitians, were prohibited from teaching or explaining the poster until after the test. The test questions were administered orally, so the subject was not required to read.

In view of the protocol, the test results were more positive than anticipated. However, they supported the view of the CDA that the educational materials being developed could not stand alone and would require careful explanation with the opportunity for follow-up learning as a part of total diabetes education. It was assumed that with education the poster would be more effective than during the test when instruction was prohibited.

Based on the awareness that type II diabetes is common among Canada's native population (20), the CDA had a special interest in the effectiveness of the GHEG poster with natives. Of the 593 questionnaires returned, 44 reported the results of testing the poster with natives. There were no significant differences between the Indians and non-Indians in the effectiveness of the poster as a meal planning tool.

The extent to which the poster is being used with native people is not known. However, dietitians working in the North report varied experiences from success to failure. Many indicate the the poster is too complex and that the foods depicted are unfamiliar to natives. The Health Services Branch, Deptartment of Indian and Northern Affairs has responded recently to the latter concern and has produced stickers with drawings of traditional native foods for use on the CDA "Good Health Eating Guide" poster. These stick on the poster or in the spaces provided in each group for such additions. Dietitians who report successful use of the poster introduce it after developing a rapport, discussing a meal plan and a few of the basic principles of diet in the treatment of diabetes.

The "Good Health Eating Guide" is now available from the CDA in English and French in three forms:

Poster - Designed for use by non-readers, the poster has drawings of each food with the name of the food printed beneath and the portion size for one choice from the group listed below the drawing. Simple measuring symbols are used with a key defining the symbols in dual measures. All the information necessary to plan a day's meals is displayed on the front of the poster with additional information modules on the back. The meal plan is blank, to be filled during diet counselling. Further detail about the poster is available, in English and French, from CDA in the "Professional Guide to the Effective Use of the Good Health Eating Guide".

Pamphlet - A compact form, without pictures, the pamphlet has more information than the poster, but less than the book. All the information necessary to plan a day's meals is displayed on a single page. The meal plan is blank, to be filled in during diet counselling.

Book - The most detailed form, the book is written at a higher reading level than either the poster or pamphlet. It lists a greater number of foods than either the pamphlet or poster and gives food portions in dual measures and by weight.

The CDA food choice system of the "Good Health Eating Guide" is conceptually an exchange system, evolved from the former "Exchange Lists for Meal Planning for Diabetics in Canada". The word choice replaces exchange which dietitians wished to change because their patients found it difficult to understand. They preferred the word choice because of its positive connotations, the suggestion to people with diabetes that they have a choice in their food selection and that the choice is theirs to make.

The "Good Health Eating Guide" poster and professional guidelines for its effective use were copyrighted by the Canadian Diabetes Association and published in 1979. They were introduced to dietitians by the provincial representatives of the Task Force presenting the new diet at conferences and workshops. Meanwhile, the work of the Task Force continued, developing the pamphlet and book to coordinate with the poster. The pamphlet and book were introduced in 1980 and 1981, respectively, and translated into French each year following. The basic tools of the revised system were complete by 1982. They are designed for the person with diabetes (or family member) to be explained by the diabetes educator.

Meanwhile, CDA developed its "Guidelines for the Nutritional Management of Diabetes Mellitus: 1980" (1) which were revised in 1984 for health professionals, setting forth the goals and strategies of diet according to the type of diabetes. Also, the Professional Health Workers Section of CDA produced "Standards and Guidelines for Diabetes Education in Canada" in 1981 (2) and these are currently undergoing a revision. These are reference tools for health professionals who teach people with diabetes and their families.

With the basic nutrition education tools available - the "Good Health Eating Guide" in three forms - and the continuing education documents for health professionals in place as mentioned above, the CDA turned its attention to the revision and development of support materials based on the Good Health Eating Guide.

All CDA educational pamphlets have been revised and new ones are being added each year. Flip charts were developed in 1984 and a new audio-visual aid "Taking Charge" is available in 1985. Each has a section on diet and diabetes.

A new cookbook, Choice Cooking, was developed by CDA and has become a best seller with over 100,000 copies in print after only two years. Another cookbook, Light & Easy Choices, was published in 1985, with CDA serving as technical adviser to the author to ensure the book's suitability for young people with diabetes.

Creative dietitians have begun to develop educational games using the "Good Health Eating Guide." (21) Ideas for food games have been developed and articles written for publication so that diabetes educators throughout Canada may learn of these ideas to the benefit of the people with diabetes whom they teach (22, 23).

The food choice values and symbols of the GHEG are a simple way to express the macronutrient composition of foods. The CDA has developed a protocol for use of the symbols by food manufacturers on selected products. Use of the CDA food choice values and symbols does not constitute an endorsement of products by the CDA. It is an effective way to expand the variety of food choices for the educated consumer with diabetes. As people with diabetes have the opportunity to attend diabetes education classes, they develop a more complete understanding of the system and its symbols. A few manufacturers are currently using the CDA symbols by permission on their products. Such use is expected to increase.

Nutrition labelling of foods is seen by the CDA as an important means of further increasing the variety of foods available to people with diabetes. In response to the federal government's proposal on nutrition labelling (Information Letter No. 641), CDA conducted a survey of its members, over 1100 of whom replied. The over 900 with diabetes responded that they strongly favour nutrition labelling and would use the information on macronutrient content to decide:

- What foods to eat;
- How much of the food they could eat safely; and
- How the food would fit into their meal plan.

CDA continues to be available to government and the food industry to develop mutually advantageous nutrition labelling. The development of a uniform format providing a core list of nutrients on food labels at point of purchase holds great promise to assist people with diabetes.

The GHEG of the Canadian Diabetes Association is used in most of Canada at the present time. Manitoba is now fully converted to the GHEG system for use in teaching people with diabetes. All but a few hospitals in Ontario have changed to the GHEG from the former CDA exchange system as stocks of printed booklets have needed replacement. All children's hospitals use the GHEG, except St. Justine's in Montreal and the Toronto Hospital for Sick Children in Toronto, where each have developed their own system with similarities to the GHEG. Throughout most of Quebec, the dietary system of L'Association du diabète du Quebec (ADQ) is used. Two exceptions are the Montreal General Hospital and the Montreal Children's Hospital, both of which use the GHEG. The revised diet manual of the Corporation of Dietitians of Quebec uses the GHEG of CDA as does the revised diabetes manual of ADQ. Both publications are anticipated in 1985, making possible a more extensive use of CDA materials in Quebec. Thus, the use of the GHEG is more uniform as compared with the CDA exchange system which was not used in Manitoba or Quebec and several hospitals in British Columbia and Ontario.

The Canadian Diabetes Association has granted permission to provincial dietetic associations to use the GHEG in their diet manuals for diabetic and energy controlled diets as follows: Alberta, British Columbia, Newfoundland, Nova Scotia, and Ontario. These provinces as well as Prince Edward Island, New Brunswick and Manitoba, use the GHEG in hospitals as well as in their public health units as the basis of information given by public health nurses. CDA has also granted permission to numerous dietitians who have used the GHEG as a basis of diets in hospital-based weight clinics.

SUGGESTIONS FOR IMPROVEMENT

Access and Funding

The greatest need for improvement in diet counselling and nutrition education services to people with diabetes and their families has two parts:

1. Greater access by the public to professional dietitians for the implementation of the prescribed diet through individually tailored meal plans and diet counselling with follow-up, and

2. Improved government funding of diet counselling services and out-patient diabetes education centres.

This is a two-fold need as the financial restrictions on hospital-based out-patient diet counselling and diabetes education programs have severely limited the number of dietitians and the time available per patient. Fee for service diet counselling is becoming more widely available, but is not accessible to the many individuals who cannot afford the fee.

To relieve the current pressure of long waiting lists resulting in delayed access to existing and limited out-patient (government funded) diet counselling, the fees of qualified dietitians in consulting practice should be covered under provincial health care plans. Such an improvement would provide people with diabetes and their families with the much needed "survival" tools of a prescribed meal plan and the basic knowledge of how to use it at home, while they are waiting to enter a diabetes education program in which they will learn about all aspects of diabetes care. Until private diet counselling is covered by government health care plans, hospital based out-patient diet counselling services (and dietitian hours) must be increased to meet the current need. Since diabetes is estimated to be increasing by six percent per year (15), the pressure on the health care system for diet counselling and diabetes education is expected to increase.

Canadian society generally accepts the self-care model in the treatment of chronic disease. By assuming the major responsibility for their own care, people with diabetes on a daily basis are replacing the potential need for three shifts of dietitians to plan, monitor and appropriately adjust food intake under changing conditions of daily living; three shifts of nurses to monitor blood (or urine) glucose levels and urine ketones, administer medications, implement careful hygiene and watch for potential problems (e.g. foot care, etc.); and three shifts of physicians to direct and coordinate all aspects of diabetes care. This is a full time job which offers no days off and requires periodic consultation with the professional diabetes care team. Accessibility to qualified health care professionals is crucial to successful diabetes self-care. Education is the means by which people with diabetes and their families gain the expertise to carry out the job of self-care. By personally accepting and successfully carrying out this responsibility, people with diabetes and their families greatly relieve the government-funded health care system which would be expected to provide this necessary and expensive life-long care if individuals did not. (24)

Continued Role of Diabetes Associations

The Canadian Diabetes Association intends to continue its supportive role to develop and provide, at minimal cost, high quality educational tools for use by health professionals and individuals with diabetes and their families. Already, CDA, in the voluntary sector, has produced a steadily increasing number of pamphlets which are free-of-charge to individuals and government funded hospitals and the over 170 diabetes education centres throughout Canada. (25) Each pamphlet is developed with the expertise of professional volunteers and reviewed by individuals with diabetes to ensure acceptability and suitability across Canada. Provision of these educational materials relieves the government funded programs of the cost of developing their own materials. It also saves precious hours of professional time which can be more effectively devoted to the diabetes education process.

The CDA has an on-going pamphlet evaluation process, carried out by volunteers, both lay and health professional, across Canada. Through this process the National Education Committee and the National Nutrition Committee of CDA update their educational pamphlets on a regular basis and identify the need for new materials to be developed. A new bilingual policy of the CDA Board of Directors calls for all new pamphlets to be produced both in English and French. Existing pamphlets will be translated and printed as funding and volunteer/staff time permit.

The major dietary education tools - the "Good Health Eating Guide" in three forms - are already available in English and French. These basic tools have been developed and continue to be produced using private-sector funds. Only the development and field testing of a prototype of the poster was funded by federal monies.

Other support materials for individuals with diabetes and their families were developed through private sector funding. Such materials include cookbooks, lists of convenience food products, manual for diabetes, and Diabetes Dialogue, the national magazine of CDA to its members both lay and health professional.

Continued acceptance and use of CDA educational materials across Canada will serve to unify the information used in diabetes education. Such unification assists people with diabetes who become confused by mixed messages from different health care providers within a community and between communities.

The Canadian Diabetes Association will continue its activities to provide, largely through funding from the private sector, continuing education for health professionals. Nutrition education pamphlets, developed by the National Nutrition Committee continue to be available and future plans include needs assessment and development of further information.

The development of the Nutrition Network of CDA by the National Nutrition Committee has greatly assisted in the two-way communication of needs and information among volunteer dietitians at all levels of CDA. The Network improves service at the Division (Provincial) and Branch levels of CDA to meet the needs of members for nutrition and food related information programs. The Nutrition Network also provides an important means by which current information is communicated to dietitians across Canada.

The needs of health professionals for continuing education are being met through the efforts of the Professional Health Workers Section (PHWS) of CDA and individual professional associations, such as the Canadian Dietetic Association. Conferences offer workshops and seminars on diabetes. Teleconferencing has been used successfully to provide dietitians with continuing education in diabetes through the coordinated efforts of Telemedicine for Ontario, the Ontario Dietetic Association and the Canadian Diabetic Association. Divisions and Branches of CDA also organize continuing education programs for their lay and professional members. The PHWS of CDA, through volunteer expertise and time, developed and published in 1981 the first "Standards and Guidelines for Diabetes Education in Canada". (2) These are now being revised through a coordinated review process involving health professional volunteers of the PHWS, Clinical & Scientific Section, National Education Committee, and National Nutrition Committee of CDA.

L'Association du diabète du Québec (ADQ) operates within Quebec to serve people with diabetes through their magazine, Plein Soleil, a diabetes education centre, Diabètaide, and committees of health professionals. The cookbook and other educational literature developed and published by ADQ are principally in French, with selected materials in English for use in Diabètaide. Efforts to improve communication and cooperation between CDA and ADQ continue to be a focus of both Associations to the benefit of people with diabetes and their families.

Multicultural Needs

To meet the needs of Canada's multicultural population, the requirements of the many ethnic communities must be assessed and addressed. This is an important need requiring a carefully coordinated effort involving the respective ethnic groups.

Acceptable translations are necessary, but not sufficient. The traditional health attitudes of the ethnic group must be respected and traditional foods included in the adaptation of dietary education materials.

The Canadian Diabetes Association is currently exploring the mutual benefits of membership in the recently formed Multicultural Health Coalition Santé Multiculturelle. Through the Coalition, contact with individual ethnic communities may be possible, including vital access to health professionals of the community. It is too soon to know whether this will prove to be an effective way to meet the needs of people with diabetes who could benefit from materials in their own language and cultural tradition.

Needs of the Non-Literate

Very little is available to assist non-literate people with diabetes. The major source of assistance is individual contact with health professionals giving information orally.

There is a need for visual and audio-visual teaching aids. Anecdotal reports from dietitians indicate that, supported by oral explanation, the Good Health Eating Guide poster is effective as a dietary tool, especially when another member of the family or a friend is available who can read.

Since 1975, CDA has made available a slide-tape series, Happy Living. It has recently been revised and replaced by a completely new series, Taking Charge - Living with Diabetes. Although not specifically designed for the illiterate, it may be useful as an adjunct to individual education. The section on diet is useful as an introduction to the Good Health Eating Guide by CDA. Audio-visual teaching aids developed in the United States are of limited usefulness in Canada due to the differences between the ADA and CDA systems of diet. There is a need for additional audio-visual materials to support diabetes education, especially related to nutrition.

Research

Current research is inadequate to allow dietitians to answer the many questions raised about the ideal diet and factors influencing behavior change and adherence to diet. People with diabetes now have the technology permitting them to monitor their own blood glucose levels in response to meals. Food related diabetes research under controlled conditions lags behind in providing answers to the increasing number of questions from people observing their own blood glucose fluctuations under the highly variable conditions of daily living. There is increasing confusion in the minds of diabetes educators and people with diabetes who question certain aspects of the current dogma.

Even if the ideal diet for the treatment of type of diabetes were known, there would remain the many uncertainties about how most effectively to assist people to make the complex behavior changes necessary to implement the diet along with the other adaptations required by having diabetes. The need for psycho-social research is as vital to diabetes education as food related research is to treatment.

Future plans of CDA include a thorough evaluation of the GHEG both as educational tool and as a tool to convey current concepts of dietary treatment. The implications of diabetes-related research demonstrating the glycemic effects of food (26) must be assessed to determine whether modifications to the system are necessary at this time.

Future Coordination With Other Diabetes Associations

Both the American Diabetes Association (ADA) and the American Association of Diabetes Educators (AADE) share the concerns expressed in the goals of the Canadian Diabetes Association: research, education, advocacy and well-being. Avenues are currently being explored to determine specific areas of concern in which efforts might be coordinated. For example, a continuing education workshop for health professionals on diabetes education is being planned jointly by the PHWS of CDA and the AADE to be held in Toronto in April, 1986. The National Nutrition Committee of CDA has an official liaison with the Nutrition Council of ADA. Discussions have already taken place concerning the possible mutual support of position statements on topics of mutual concern. When the Good Health Eating Guide is revised by CDA, the possibilities of coordinating changes to bring the CDA and ADA systems of diet into line will be explored.

Summary

The recommendations for improvement in the nutrition education of people with diabetes in Canada are summarized as follows:

1. Greater access by the public to the services of professional dietitians through the extension of government health care plans to cover diet counselling by professional dietitians is necessary to provide the prescribed meal plan, a basic tool in the treatment of diabetes.

2. Greater access by people with diabetes and their families to self-care programs through increased government funding of new and expanded diabetes education centres is needed to implement the prescribed diet along with the other aspects of diabetes self-care.

3. Additional opportunities must be developed and health care professionals encouraged to participate in continuing education to improve and update their knowledge and skills in diabetes care and education.

4. Continued assessment of the needs and the development by the private sector, through the Canadian Diabetes Association and L'Association du diabète du Québec, of educational literature for use in hospital-based clinics and diabetes education centres is required to provide a unified information in diabetes care.

5. Increased partnership of the voluntary sector with government in exploring the development and provision of diabetes education materials for specific ethnic groups is needed to serve Canada's multicultural society.

6. Additional audio-visual teaching tools are needed, especially related to nutrition and diabetes and for the non-literate.

7. Further research is needed in several areas related to diabetes education:
   (a) food related research to address questions about how to use food more appropriately in the management of diabetes;
   (b) psychosocial research to address questions about how people change and what factors influence their acceptance of dietary and other diabetes self-care routines; and
   (c) educational research to address questions about how people learn and what tools and approaches are most effective in teaching people with different learning styles and of different ages and ethnic backgrounds.

8. Closer communication is necessary among groups sharing a common interest in diabetes education to explore possible avenues of collaboration and coordination in the development of educational materials and programs to promote diabetes self-care.

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DIABETES EDUCATION PROGRAM FOR ALLIED HEALTH PROFESSIONALS

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Persons with diabetes has the right to accurate, comprehensive, and up-to-date information from the health professionals involved in their care and management.

As stated in the American Diabetes Association Policy statement on "third-party reimbursement for out-patient education and nutritional counselling" -

> "- The health of persons with diabetes is dependent upon control of hyperglycemia and the early treatment of complications. Studies have shown that education and self-care programs lead to reductions in hospital days and associated costs.
> - continuing patient education for self-management is an integral component of health care. Persons with diabetes have the right to available, accessible, and affordable patient education."

While standards and guidelines for diabetes education centers were clearly outlined by the professional health workers sections (PHWS) of the Canadian Diabetes Association (CDA) in 1980, these are presently under revision and a five year plan has been established to implement the standards and guidelines. There has been very little established for the education of the health professional involved with the education of diabetics.

This paper will address the ideal method of educating the health professional dealing with the education of the diabetic individual.

The Ideal Method of Training for the Diabetes Educator in Canada

Definition of Educator's Role:

In order to understand better the extent of work required to educate all health professionals dealing with diabetics one must ascertain who these individuals are. Essentially only those in health agencies will be considered as health professionals. This itself includes:

- dietitians, nurses, social workers, physiotherapists, occupational therapists, psychologists, psychiatrists, and pharmacists to name a few.

The health agencies involved included: Hospital wards, all out-patient clinics, nursing homes, convalescent homes, senior residences, home care nursing programs, local pharmacies, school nurses, staff health services (at the place of employment), prisons and others.

Ideally all of these health professionals must be informed with basic information on diabetes management. Programs must be designed to enhance the educational levels of all educators in the field of diabetes and should reflect the multidisciplinary nature of diabetes management. Courses should range between the most basic information to the most advanced.

The definition of a diabetes educator in the diabetes center must be clarified. Is the educator to be only a teacher or are they to be involved in the day-to-day management of the diabetic's control? Specific guidelines must be defined for each position. A method of evaluation of the individual's performance must be established. If necessary a "delegated acts" form must be signed by the medical advisor, if patient management is involved.

Training of the Health Professional

A diabetes educator must have a multifacetted background. They should have some skills in areas other than those specific to their profession such as interviewing, counselling, and education (both teaching and learning abilities of different ages at a variety of stages of diagnosis).

A standard program for the education of the diabetes educator should be established in one or two areas of the country. It would be most acceptable if the program was 'incorporated into a university affiliated hospital with a post-graduate program or similar agency. The curriculum should include:

Classifications of Diabetes
Review of Pathophysiology
Adult onset Diabetes
The Child with Diabetes
Home Glucose Monitoring
Living with Diabetes
Diabetes Nutrition Overview
Human Sexuality and Diabetes
Psychological Adjustment
Coping with Stress
Medications
Medications that Affect Blood Glucose
Biogenics
Advanced Concepts of Dietary Management
Dietary Calculations
Pregnancy and Diabetes
The Infant of a Mother with Diabetes
Current Research
Exercise and Diabetes
Aerobics
Footcare for Diabetics
Diabetes and the Eye
Diabetes and the Kidney
Neurological Problems in Diabetes
Patients with Diabetes
Care of the Diabetic in the Hospital
New Technologies and Management
Resources and Services
Teaching the Diabetic While in the Hospital
Kidney and Pancreas Transplants
Living with Diabetes

During this week-long workshop the participant has an opportunity to live with diabetics in order to reinforce ideas and techniques learned during the workshop.

The practicum: (optional - one week duration)

- Developing Behaviorial Objectives
- The Use and Development of Audiovisual Aids
- Evaluation
- Interviewing and Counselling Techniques
- Teaching Experience:
  - Videotaping
  - Urine Testing
  - Mixing Insulin
  - The Injection
  - Problems with Injections
  - Exercise and Diabetes
  - Hypoglycemia
  - Hyperglycemia
  - Emotions and Diabetes
- Teaching Critiques
- The Interview-Clinical Experience
- Teaching Rounds
- Team Conference
- Examination of the Basic Diabetes Material
- Debriefing

A similar program can be adapted for all health professionals dealing with diabetes.

The American Association of Diabetes Educators (AADE) is currently working on the first steps of standardization with an application to the American Nurses' Association for accreditation as a provider and as an approver of continuing education (a paper presently in the draft stage). The reason that the Nurses' Association is being approached first is that they are currently reviewing accreditation.

The purpose of this paper by AADE is - "The American Diabetes Association of Diabetes Educators, as a professional organization, has a responsibility to foster high professional standards in diabetes education and in the dissemination of information and assistance to clients. We have a responsibility to stimulate educational research, encourage interdisciplinary communication and cooperation and to address issues relating to diabetes education. We have the responsibility to identify, for the consumer, the competencies and excellence of the professionals in practice."

In brief the paper states that it is important that the basic and advanced levels of education be carried out in at least the following ten areas:

1. Pathophysiology of Diabetes and Complications:
   - to include physiologic, immunologic, genetic and other factors thought to be associated with the pathophysiology of diabetes.
2. Nutritional Aspects of Diabetes:
   - to include nutritional management of both type 1 and type 1I - use of the good health eating system, the use of fiber, etc.

3. Medications Used for Management of Diabetes:
   - to include both insulin and oral agent therapy, with new trends. The effects of other medications on the management of diabetes.
4. Self-Management Practices:
   - to include methods of self-management i.e. blood glucose monitoring, urine testing, diet control, regular exercise, etc. Discussion on the role of behavior sciences and related research - compliance and motivation techniques.
5. The Psychosocial Aspects of Diabetes and Its Complications:
   - to include the adaptation process, the impact of the diagnosis on the individual and the family, and living with the complications of diabetes, cultural anthropology, sociology, psychology, and mental health research is essential.
6. The role of Exercise in Diabetes Management:
   - to include the role of exercise physiology and physical therapy in the management of diabetes.
7. Teaching and Learning Principles:
   - to include education theory-related to both patient and staff education. Information drawn from the fields of education, computer technology, social and cultural anthropology, and psychology.
8. Team Approach to Education:
   - to include organizational behavior.
9. Management of Diabetes Education Programs:
   - to include program design and structure, marketing strategies, and evaluation techniques.
10. Research and Publication Skills:
    - to include methods of research and information on writing for publication.

It is recommended that each of these areas listed be given a time allotment of 50-60 minutes with additional time given for practicum and evaluation.

A method for evaluation of the health educator's performance should be incorporated with the program and carried out initially every six to twelve months. Follow-up education, i.e. continuing education workshops attendance, should be part of the evaluation.

In Canada the Professional Health Workers Section of the Canadian Diabetes Association have similar plans in order to meet their purpose and goals, which were revised in 1982 to read:

Purpose: The Professional Health Workers Section of the Canadian Diabetes Association is dedicated to helping people concerned with diabetes through educational efforts and information of the highest quality.

Goals:

1. The PHWS will develop and promote resources for the use of individuals with an interest in diabetes mellitus and related disorders.
2. The PHWS will influence policy and decision makers concerning the needs of the diabetic community.
3. The PHWS will establish guidelines for standards of practice for health professionals involved with diabetes education.

Funding for the PHWS Project - to develop a model of practice for health professionals for the education of diabetics -- is currently being sought. In the meantime the PHWS has been observing the American plans and methods very closely and is currently working jointly on the first North American Symposium to be held in Toronto in 1986. The Symposium is geared to such issues as certification, continuing education, motivating the health professional to higher levels, reimbursement policies, national standardization and the implementation in varied settings, and other pertinent concerns of the innovative caregiver.

The training of the health professional can be better enhanced if certain items are also incorporated in the long-term strategies such as: -

- A national central resource base with all the pertinent and up-to-date information and educational tools used across the country should be compiled and easily accessible. This would be comparable to the diabetes clearinghouse in the United States.
- All national workshops should be coordinated from one central area in order to avoid duplication of efforts. A five year agenda of conferences, workshops, symposia, etc. is suggested. If accredication is in the future each program can be allotted credits from the central agency.
- Continuing education models can be developed and distributed in a correspondence course fashion. The AADE is doing this at the present time in preparation for the certification of health professionals.

Diabetes education is a major factor in changing the health behavior of the diabetic population, which, in turn, minimizes the burden on the health care system. Therefore those health professionals given the responsibility of patient management and education must be properly prepared for the task and obliged to keep abreast of new developments and methods. The proper education of these individuals is critical.

The Actual Situation for the Training of Diabetes Educators in Canada to date:

In a brief survey of the Canadian diabetes community it appears that there is no established program for the health professional interested in diabetes management or teaching. No college or university program was found for the initial or the continuing education up-date of the educator. There are many conferences, workshops, and symposia available but the curricula are essentially for the experienced educator and does not necessarily offer continuity of data. Some programs have a tendency to be redundant. These programs are also dependent on interest of the particular regional universities' faculties and the availability of funding. Drug companies will often sponsor a meeting which adds the dimension of their own individual interests.

The criteria for hiring a diabetes educator varies within a city as well as from province to province. No standard job description has been established. For the most part diabetes educators are being "trained on the job". Therefore the educator is generally being influenced by the particular "School of Thought" of the individual in charge of the program, usually the medical advisor, who is not necessarily trained in patient education.

In essence training of the diabetes educator in Canada is strongly influenced by individuals and has little national direction. Information for diabetics varies within a city as well as from province to province.

Conclusions from the Data Presented for the Training of The Diabetes Educator

Let it be said that:

- there is no formalized, ongoing, approved program, nationally or provincially, for the education of health care professionals in the area of diabetes.
- individual standards are the criteria for training of the diabetes educator.
- there is a need for a standard, nationally approved, program for the diabetes educator in order to offer consistent information to the nomadic Canadian diabetes community.

It is via the mode of patient education that diabetic individuals will become aware of their rights as consumers and search out the optimum care of their lifelong condition, which is ultimately their responsibility.

Recommendations for the Training of Diabetes Educators:

It is recommended that a national agency be assigned to establish and coordinate a training program for diabetes educators. The PHWS would be an appropriate group due to their work both with the standards and guidelines for diabetes education centers in Canada and with the American Association of diabetes educators group in the United States.

It is also suggested that long-term strategic planning of the project be formulated to assess the objectives and need for change as work progresses. Shared goal setting and evaluation with other health care organizations, i.e. AADE, Canadian Public Health Association, Canadian Council of Hospital Accreditation and Professional Licensing Agencies should be established. This will be necessary if accreditation is decided upon.

A national resource base should be set up in order to have a central up-to-date data base to facilitate research and continuing education.

It cannot be over-stated that diabetic individuals must manage their own condition and we as health professionals must be properly trained in order to assist them to live with the reality of diabetes.

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RESEARCH

Summary and Recommendations

1. The two major goals of diabetes research are defined as
   (a) to understand the basic and fundamental processes involved in the etiology and pathogenesis of diabetes and its complications.
   (b) to develop and evaluate improved methods for preventing and treating diabetes and its complications.

2. A survey of research topics related to diabetes was done. These areas include:

   (a) etiology of diabetes mellitus;
   (b) epidemiology of diabetes mellitus;
   (c) hormone biosynthesis and actions;
   (d) insulin secretion and metabolism;
   (e) management of diabetes including diets, insulin therapy, oral hypoglycemic agents, exercise, education, and pyschosocial aspects;
   (f) alternative modes of treatment presently regarded as experimental - transplantation and immuno-therapy;
   (g) complications of diabetes;
   (h) pregnancy and fetal developments.

3. The present areas of research activity in the 1983-84 in Canada were outlined.

4. The current (1983-84) manpower in diabetes research in Canada and the number of trainees required to maintain the status-quo were discussed. To replace the 112 investigators, the number of trainees (assuming 11 "graduates" annually amongst other things) is 52, assuming only 80% of these new investigators receive funding, the requirement is 65 trainees each year. Assuming that $23,231 (a conservative estimate) are needed for each trainee, the amount of funds needed to maintain 65 trainees would be $1,510,000.

5. The need to create faculty positions for these new diabetes investigators is recognized. So is the need to create career development awards by the various granting agencies.

6. The present situation as perceived by 18 researchers was outlined:

   (a) an insufficient number of well trained investigators, and
   (b) inadequate funding of operating grants.

7. Instead of supporting targeted research it was recommended that agencies should:

   (a) support those diabetes researchers of excellence irrespective of field of interest;
   (b) introduce new areas of diabetes research excellence;

(c) redirect the interest of established investigators in other fields to do diabetes research.

8. The reports of "The Medical Research Council/Royal College of Physicians and Surgeons (Canada) joint Task Force on Clinican Scientist was discussed. Formed in 1982, this Task Force had the following terms of reference:

   (a) "to make definite proposals to the sponsoring bodies on methods for promoting the entry into research, and on the research training and research career opportunities for clinican scientists";
   (b) "to examine how the programs of Medical Research Council and the Royal College of Physicians and Surgeons could be adjusted to support the training of clinician scientists".

The report and its 15 recommendations were discussed.

9. The formation, administration, funding and activities of the three Canadian Diabetes Centres were reviewed by George Molnar. These centres are as follows:

   (a) Banting and Best Diabetes Centre at University of Toronto;
   (b) Muttart Diabetes Research and Training Centre, University of Alberta, and
   (c) Julia McFarlane Diabetes Research Units at University of Calgary.

10. The psycho-social aspects of diabetes management and the need for research in this area were presented by Isabel Burrows, and discussed.

11. The various types of research supported by pharmaceutical companies was discussed; these include goal directed research (development and clinical trials of drugs developed by the company) and other research (for example post-doctoral fellowships).

Recommendations

1. A suitable sub-committee of the National Task Force on Diabetes Mellitus should be established to analyze the implications and the means of implementing the following recommendations.

2. Training grants supported with new funds obtained from government sources should be made available to suitable programs which can recruit potential trainees in a more assured manner.

3. Diabetes Canada should direct a substantial portion of the funds raised to the support of scholarships awards analogous to the Medical Research Council scholarship awards.

4. The issue of coordinating funding between the Medical Research Council and national volunteer organizations should be addressed.

5. The National Diabetes Task Force should support the recommendations of the MRC-RCPSC joint Task Force on Clinican Scientists.

6. The Royal College of Physicians and Surgeons should reduce the amount of clinical training deemed necessary for specialties certification so as to permit trainees to pursue research endeavours in various areas, including diabetes mellitus.

7. The base salary of established clinician scientists should be sufficient to allow them to maximize their research time.

8. Diabetes research and training centres of excellence should be encouraged to develop in Canada. These centres should share relatively uniform guidelines with regards to objectives so that quality assurance of their programs can be done. Extra-mural endowment funding together with governmental (federal and/or provincial) may be a feasible approach in setting up these potential centres.

9. Psycho-social aspects of diabetes management should be included among the various topics of diabetes research.

10. A closer collaboration in diabetes research between industries and universities as well as institutions involved in research should be promoted.

THE CURRENT STATUS OF DIABETES RELATED RESEARCH IN CANADA

M.H. Tan, M.D.

Introduction

Canadians have been doing diabetes research for many decades. However, the extent of Canadian diabetes research, in terms of funding and personnel support, over the years has not been well documented. Nor has the magnitude of short funding of diabetes research in Canada been well defined. These shortcomings were recognized by the Canadian Diabetes Association (CDA) about five years ago when its Research and Advocacy Committee endeavoured to solve both problems, but with limited success. In 1982-1983 the CDA Research Council was making preparations to make a second attempt to solve these problems when Diabetes Canada and the Medical Research Council (MRC) jointly appointed a task force "to study the present state and long-term needs of diabetes research in Canada". This report summarizes some of the findings of this task force, the Diabetes Canada Research Advisory Committee*.

Since 1971 the CDA has been supporting diabetes research in Canada. Initially the financial support was modest. The creation of the Charles H. Best Fund for Research, Discovery and Education in 1975 gave great impetus to the CDA support for diabetes research. This report also outlines the magnitude and type of research support provided by the CDA between 1976 and 1984.

Methods

The Diabetes Canada Research Advisory Committee obtained information on funding of diabetes-related research in Canadian medical schools for the academic year 1983 - 1984 by a questionnaire method in December, 1983. The questionnaires, seeking information on operating and equipment grants as well as personnel awards were completed by an individual at each medical school. This individual was selected because of his/her familiarity with diabetes related topics. From this data base (obtained from 15/16 medical shcools), the funding and type of diabetes related research were determined.

Information on the CDA supported research was obtained from the CDA.

Results

Table 1 shows the funding of operating/equipment grants and personnel awards in each of the fifteen medical schools. Of the total of $7,435,177 spent on diabetes-related research, 24% was received by the University of Toronto, 20.5% by McGill University, 11.3% by the University of Alberta, and the rest by the remaining schools. Of the total only 14.2% was spent on personnel support. For operating and equipment funding, 46.7% was provided by MRC, 12.2% by CDA, 3.3% by the Juvenile Diabetes Foundation International, and 37.6% by provincial, local and other sources. There were 112 investigators who received a total of 176 grants. There were 36 graduate students - 10 at the University of Alberta, 6 at the University of Toronto, and 5 at the University of Montreal. Of the 30 postdoctoral fellows, 9 were at the University of Toronto, 7 at the University of Calgary, and 4 at McGill University.

Table 2 shows the types of research done by investigators across the nation. The majority of the research dealt with basic science (37.5%) and pathophysiology (30%) of diabetes mellitus.

Table 3 shows the research funding provided by the CDA between 1976 and 1984, where the total funding increased from $139,479 to $1,121,714. This represents an increase of 704.2% over eight years! The number of grants funded increased from 12 (1976) to 34 (1984). During this period, the CDA supported 209 projects.

Table 4 shows the CDA research funding according to university during two periods of time: 1976 - 1980 and 1981 - 1984. The number of grants received increased in twelve universities, decreased in three, and remained unchanged in one university.

Table 1
Diabetes Related Research Funding 1983 - 1984 (1)

University	Operating and Equipment Grants	Personnel Support	Total
Alberta	$ 633,263	$ 208,660	$ 841,923
British Columbia	288,172	10,000	298,172
Calgary	355,178	161,500	516,678
Dalhousie	222,750	--	222,750
Laval	113,900	29,500	143,400
Manitoba	93,558	9,400	102,958
McGill	1,407,588	118,000	1,525,588
McMaster	32,000	22,400	54,400
Memorial	143,200	25,000	168,200
Montreal	563,038	55,000	618,038
Ottawa	107,000	54,000	161,000
Queens	130,162	22,000	152,162
Saskatchewan	142,802	18,900	161,702
Toronto	1,513,201	264,350	1,777,551
Western Ontario	634,655	56,000	690,655
Total	$6,380,467	$1,054,710	$7,435,177

Table 2
Diabetes-Related Research 1983 - 1984 By Topics(1)

Topic	Project (%)	Investigators (%)
1. BASIC SCIENCE	37.5	38.5
2. PATHOPHYSIOLOGY	30.0	23.7
3. MANAGEMENT	10.0	11.5
4. COMPLICATIONS	9.4	11.5
5. TRANSPLANTATION	7.5	11.5
6. GENETICS-EPIDEMIOLOGY	3.1	4.1
7. OBESITY	2.5	3.3

Table 3
CDA Research Funding 1976 - 1984

Year	Total Funding	Number Of Grants	Average
1976	$ 139,479	12	$11,623
1977	$ 141,344	12	$11,779
1978	$ 227,091	15	$15,139
1979	$ 362,174	22	$16,462
1980	$ 564,895	27	$20,922
1981	$ 630,134	26	$24,236
1982	$ 806,678	31	$26,022
1983	$ 981,642	30	$32,721
1984	$1,121,714	34	$33,109
TOTAL	$4,975,151	209	

Table 4
CDA Research Funding

	University	1976-1980	1981-1984	Total
1.	British Columbia	4	5	9
2.	Alberta	5	7	12
3.	Calgary	4	3	7
4.	Saskatchewan	2	5	7
5.	Manitoba	4	5	9
6.	Toronto	27	34	61
7.	Western Ontario	7	8	15
8.	Ottawa	11	4	15
9.	McMaster	4	0	4
10.	Queens	2	8	10
11.	McGill	6	14	20
12.	Montreal	2	7	9
13.	Laval	3	7	10
14.	Dalhousie	4	4	8
15.	Memorial	3	9	12
16.	Waterloo	0	1	1
	Total	88	121	209

Table 5
CDA Supported Research By Topic 1976-1984

1.	ETIOLOGY/GENETICS		
	(a) HLA	3	
	(b) BB rat	4	
	(c) Virus	2	
	(d) Immunology and others	5	
		14	14
2.	PATHOPHYSIOLOGY		
	(a) Insulin secretion	10	
	(b) Insulin action	12	
	(c) Insulin receptors	6	
	(d) Glucagon, Gut hormones	11	
	(e) Glucose metabolism	12	
	(f) Basic biochemistry	17	
	(g) Others	2	
		70	70
3.	COMPLICATIONS		
	(a) Eye	9	
	(b) Kidney	4	
	(d) Nervous system	14	
	(d) Macrovascular	9	
	(e) Others	5	
		41	41
4.	MANAGEMENT		
	(a) Diet	11	
	(b) Insulin	7	
	(c) Exercise	20	
	(d) Oral agents	1	
	(e) Education	1	
		40	40
5.	PSYCHOSOCIAL	2	2
6.	CONTROL	2	2
7.	TRANSPLANTATION	4	4
	TOTAL		175

Table 6
CDA Research Funding (Millions)

	1982	1983	1984
REQUESTED	$1.86	$2.15	$1.76
APPROVED	$1.27	$1.38	$1.35
FUNDED	$0.85	$0.98	$1.12
SHORT FUNDING	$0.42	$0.40	$0.23

Table 5 shows the CDA supported research by topic from 1976 - 1984. Most of the grants were for research in the pathophysiology (70), complications (41) and management (41) of diabetes mellitus.

Table 6 shows the CDA research funding in 1982 - 1984. For each year the amount requested represented the total amount of funds requested by all submitted grant applications. The amount approved represented the total amount of funds of all applicants evaluated by a peer review process to have scientific merit worthy of funding. The amount funded represents the amount of funds provided to successful applicants as approved by the Board of Directors. This amount depends on the funds available for research support for that particular year. The short-funding represents the amount that would be needed to fund the remaining grants judged to have scientific merit but not funded because of insufficient funds.

Discussion

As expected, the amount of funding received for diabetes related research by each medical school varied considerably in 1983 - 1984. Three universities dominated the scene during that year - University of Toronto (24%), McGill University (20.5%) and University of Alberta (11.3%). In the next few years, the amount received by the Alberta medical schools will increase partly because of the impact of the Alberta Heritage Foundation for Medical Research programme which provides considerable local funding and attracts more investigators to these two centres. It would not be surprising that the large centres will become bigger, and the small centres remain unchanged or become smaller.

The amount and proportion of funds received for diabetes related research from all sources will undoubtedly vary from year to year. In 1983 - 1984, the MRC was the major provider (46.7%) with the CDA, Canada's largest volunteer organization concerned with diabetes, second (12.2%). A significant amount of funding for such research was also provided by provincial, local and other sources.

There are three Diabetes Centres in Canada: (a) the Banting and Best Diabetes Centre at the University of Toronto, (b) the Julia McFarlance Diabetes Research Unit at the University of Calgary, and (c) the Muttart Diabetes Research and Training Centre at the University of Alberta. The funds for these Diabetes Centres are generated extramurally. Similarly, Connaught Laboratories spent considerable intramural funds in diabetes research. Details on these have been previously reported.[1] Other pharmaceutical companies are beginning to conduct multicentre trials in diabetes related research in Canada. Details on these were not available in 1983.

As for operating/equipment funding, there is considerable heterogeneity in the distribution of personnel support for diabetes related research. Again three universities dominated the scene: the University of Toronto (25% of total funds, six graduate students and nine fellows), the University of Alberta (19.8% of total funds, ten graduate students and three fellows), and the University of Calgary (15.3% of total funds, two graduate students and seven fellows).

Only 14.2% of the total diabetes related research funding was spent on personnel support. Considering that between 15 - 20% of all MRC funding is for personnel support, this percentage is low. In the present analysis, no distinction was made between clinical and research fellows. Hence the percentage of the funds allocated for training future diabetes researchers was relatively low. This assumption was supported by the evidence that MRC allocated 7.6% of its total funds granted for diabetes related research as stipends for trainees. The CDA allocated only 3.2%. These formed the basis of the recommendation that more funds should be spent by Diabetes Canada for personnal support.

The data on the research funding provided by the CDA are limited in that it focuses only on one organization. However, it is the only data presently available to show the changes in funding of diabetes related research over a period of time. The CDA presumably began funding diabetes related research in 1971 and available data show the support to be rather small: 1971 ($64,849), 1972 ($10,000), 1973 ($50,210), 1974 ($43,850) and 1975 ($36,368). After the formation of the Charles H. Best Fund in 1975, the little acorn suddenly became an oak tree, and has continued to grow ever since. Between 1976 and 1984, it grew 704.2%! Despite this growth there was significant short funding of diabetes related research requested of the CDA during 1982 - 1984. In 1982 and 1983 this amounted to about $420,000 and $400,000 respectively. During these two years the cut-off point for funding was high because of shortage of research funds. In response to this need and challenge, the CDA allocated more funds for research in 1984 so that the short funding was only about $230,000.

Many universities received more grants from CDA during the period of 1981 - 1984 compared with 1976 - 1980. The total number of CDA grants have also increased from 12 in 1976 to 34 in 1984. Both these reflect increasing diabetes related activity at Canadian medical schools. The mean amount for each grant has increased from $11,623 in 1976 to $33,109 in 1984. This reflects the increasing cost of doing research and the scope of the application. Beginning in 1984, the CDA adopted the policy that the maximum amount to be granted per application will be $40,000. This decision was made so as to fund as many investigators as possible each year.

Tables 2 and 5 show the diabetes related research by topic in 1983 - 1984 and between 1976 and 1984 respectively. Both show that pathophysiology, complications and management accounted for the majority of grants supported. These observations should not be overinterpreted for many reasons: (a) the categorization was based on the short title of the grant without reviewing the actual grant application; (b) the distribution of areas of research reflected areas of research activity world wide 3 - 4 years prior to each of the periods when the experiments were planned; (c) not all areas of diabetes related research are of equal importance; and (d) the listed projects were those funded, not all those submitted.

In 1976 the CDA research funding was 8.9% that of ADA and in 1984 it was 28.7% (R. Bolan: personal communication). Such international comparisons must be interpreted with caution for cost elements (salary support, overhead, etc.) are different in different organizations. Comparisons of national support for diabetes research are difficult to make for various reasons. Different nations have different degrees of government research in diabetes. For example, the National Institute of Health in the United States carries out a very significant amount of diabetes research whereas there is no similar government involvement in Canada. Furthermore, involvement of pharmaceutical companies in diabetes research will vary between nations.

In Canada the total direct expenditure on biomedical research for 1983 - 1984 was estimated to be $270 million (Dr. L. Slotin: personal communication). If this was correct, 2.7% of these dollars were spent on diabetes related research. No comparison of research support for diabetes can be made with other disease (e.g. heart, kidney, liver disease, etc.) research support because data for the latter are not available.

Following the recommendation of the task force, Diabetes Canada recently initiated a Diabetes Canada Scholar and Diabetes Canada postdoctoral programme. These initiatives will hopefully meet the short-term needs of diabetes related research personnel needs. Plans to meet the long-term needs must also be started soon.

It is clear that the knowledge uncovered by research yesterday has made possible our understanding of diabetes today. Unless we continue the quest for new information about diabetes, there will be no possibility of a cure for diabetes tomorrow. We must continue to support research for it makes the difference between no cure and the possibility of a cure for diabetes tomorrow. Perhaps, one day, there will be another monumental contribution from Canada to diabetes, one that will have as much impact as that made by Banting and Best in 1921.

REFERENCE

1. The Diabetes Canada Research Advisory Committee: Diabetes Related Research in Canada. Can Med Assoc J 1985, 133:103-105.

*FOOTNOTE

The members of the Diabetes Canada Research Advisory Committee are: Drs. J.L. Chiasson, E. Colle, G. Hetenyi Jr., G.D. Molnar, J.M. Roxburgh, L.A. Slotin, B. Zinman and M.H. Tan (Chairman).

DIABETES RESEARCH IN CANADA: PROBLEMS AND PROSPECTS

Geza Hetenyi, M.D. and Barry I. Posner, M.D.

Introduction

It is well accepted that research, giving rise to new knowledge, has major impact on the practice of clinical medicine. It is our thesis that Canada must contribute its full share to worldwide biomedical research efforts because:

1. The efforts to understand the world and shape it in the interests of man represent a central feature of an enlightened civilization.
2. It is in our self interest to have a strong biomedical community in Canada since:
    (a) this assures a ready and deep exchange of ideas and developments with other parts of the world.
    (b) such a community is essential for quality teaching of our health professionals and plays a key role in setting standards for optimum health care.

Canada has contributed much to the understanding and treatment of Diabetes Mellitus. Though insulin was discovered over 60 years ago this complex disease or family of diseases still poses a serious challenge to us all. It afflicts about 600,000 Canadians and probably costs our economy around $800,000,000 per year in medical costs, time lost from work and premature death. It is one of the leading causes of blindness and kidney failure, and is responsible for a significant percentage of heart attack and strokes. Approximately 25% of patients have disabling neurological complications. Thus the complete understanding and proper treatment of Diabetes Mellitus will have enormous implications for human welfare.

The two major goals of modern diabetes research are:

1. To improve our understanding of basic and fundamental processes involved in initiating and maintaining the disease and its complications.
2. To develop and evaluate improved methods for preventing and treating diabetes and its complications.

The Ideal Situation

Under ideal circumstances it would be desirable to pursue a wide range of research endeavours related to the understanding, prevention and treatment of Diabetes Mellitus. The following list is meant to be illustrative, and we emphasize that new research initiatives, at present unforeseen, may emerge as important areas of concern.

1. Etiology and Epidemiology

(a) Insulin Dependent Diabetes Mellitus (IDDM)
    (i) Annual and Geographic differences in incidence.
    (ii) Continuing assessment of natural history.

(iii) Relation between specific HLA antigens and etiopathogenesis of IDDM.
(iv) Role of islet cell antibodies and cell-mediated processes in causation and clinical course.
(v) Genetic studies, with molecular biologically developed probes, of precise gene defects in the HLA region with which the disease is associated.
(vi) Studies of autoimmunity - its genesis and control - especially in appropriate animal models viz. the BB rat.

(b) Non Insulin Dependent Diabetes Mellitus (NIDDM)
(i) Identification of markers for prediabetic state and thus determine mode(s) of inheritance.
(ii) Significance of restriction enzyme polymorphism in the flanking region of the insulin gene.
(iii) Natural history and predictive value of impaired glucose tolerance.
(iv) Understanding of insulin action and hence nature of insulin resistance.
(v) Studies on the relationship between defects in insulin secretion and insulin action.
- Prospective studies in defined populations.
- Biochemical studies relating the 2 processes.
- Animal models in which to carry out such studies.

(vi) Insulin action in vivo in man - estimates of action in different target tissues including muscle - in health and NIDDM.

(c) Improved therapy of diabetes mellitus.
- More effective approaches to weight loss in obesity.
- Effect of different dietary CHO and fiber regimes on metabolism.
- Relation between hyperinsulinemia (accompanying peripheral insulin administration) and diabetic control and complications.
- Role of physical training in management.
- Effect of oral hypoglycemic agents at cellular level.
- Analysis of oral hypoglycemic agent responders and failures in order to determine how best to employ these drugs.
- Evaluation of immunological modalities for the treatment of type 1 diabetes mellitus.
- Assessment of techniques for educating both health care professionals and patients in the treatment of obesity.

2. Hormone Biosynthesis

(a) Increased study of insulin gene mutations and polymorphisms and their incidence in Diabetes Mellitus.
(b) Mechanisms by which glucose and other substances stimulate gene transcription.

(c) Cell biology of biosynthesis and secretion including: mechanism(s) for segregating secretory proteins, intracellular protein sorting and transport, enzymes and physical structures involved in processing etc.
(d) Nature and function of peptides which regulate pancreatic secretion including studies of their interaction with neuroregulation.
(e) Development of methods for getting insulin gene expression in cells suitable for transplantation into patients.
(f) Production by biotechnology of proteins and peptides related to diabetes research including human growth hormone and the insulin-like growth factors.

3. Insulin Secretion and Metabolism

(a) Biochemical mechanisms by which neural, hormonal, metabolic and pharmacologic influences control insulin secretion.
(b) Evaluation of islet cell-cell interactions including islet cell anatomy, vasculature, heterogeneity, nerve communication and gap junctions.
(c) Determination of factors involved in regulating islet cell mass.
(d) Study relation between islet cell surface proteins and secretion (viz. by use of monoclonal antibodies against cell surface proteins).
(e) Development of animal models for studying insulin secretion.
(f) Evaluation of the kinetics of insulin clearance and metabolism in animal models and humans.

4. Hormone Action

Further studies are needed to:
(a) Define the role of the insulin receptor kinase in hormone action including the determination of activation mechanism and suitable physiologic substrates.
(b) Employ genetic methods to dissect out receptor structure-function relationships (viz. using techniques of mutagenesis).
(c) Assess mechanism by which insulin action is modulated by other hormones.
(d) Determine mechanism by which glucose transporters are shifted from intracellular to cell-surface domains.

5. Insulin Therapy

(a) Determine relationship between tight control and the initiation and evolution of complications.
(b) Develop insulin preparations suitable for use in external and implantable insulin delivery devices.
(c) Evaluate different routes of insulin administration re control of metabolic disturbances in Diabetes Mellitus.

(d) Development of glucose sensors to provide a "closed loop" portable (miniaturized) system for precise regulation of blood glucose.

6. **Transplantation as an alternative to insulin therapy**

(a) Improve techniques of pancreatic transplantation.
(b) Assess and try to prevent cell-mediated attack on transplanted islets.
(c) Develop technology for large-scale isolation of human islets to be used clinically.

7. **Complications**

(a) Study the relationship between metabolic control and complications.
(b) Increase understanding of nephropathy by:
    (i) Determining the role of vasoregulation and glomerular capillary wall function in the pathology of hyperglycemic states.
    (ii) Assessing the regulation of synthesis and degradation of glomerular matrix components in normal and diabetic states.
(c) Investigate pathogenesis of retinopathy by:
    (i) Characterizing defects in blood ocular barriers.
    (ii) Delineating role of polyol pathway and glycosylated proteins.
(d) Study the cardiovascular complications by:
    (i) Assessing relation between hyperinsulinism and atherosclerosis.
    (ii) Studying platelet interactions with the vessel wall and effects of diabetes on this.
    (iii) Studying the influence of insulin, glucose and counter-regulatory hormones on vascular metabolism.
(e) Study the impact of insulin and its deficiency on the nervous system:
    (i) Studying the roles of insulin and glucose in both central and peripheral nervous system metabolism.
    (ii) Evaluating neural pathways and biochemical processes involved in appetite regulation, and role of insulin in regulating this system.
    (iii) Performing clinical trials with aldose reductase inhibitors.
    (iv) Assessing structure-function relationships in diabetic neuropathy by repetitive sampling of peripheral nerves for structural and biochemical analysis.

8. **Pregnancy and Fetal Development**

(a) Study role of insulin and insulin-like growth factors in fetal growth and metabolism.

(b) Assess role of insulin and hyperglycemia in the development of congenital anomalies.
(c) Examine more thoroughly various genetic factors which may contribute to congenital malformations (viz. family history, HLA type etc.).
(d) Establish ways of assessing presence and severity of congenital anomalies in the early phase of diabetic pregnancies.

Current Situation in Canada

1. Areas of Research Activity

Data have been collected by the Diabetes Canada Research Advisory Committee on the number of projects and their distribution among different fields of interest (1). Since some researchers may direct more than a single project and occassionally there are two principal investigators directing a project, the number of projects indentified differs from the number of researchers active in diabetes related research.

The distribution of 155 projects identified by the survey is shown below:

Type of Project	Number	%Total
Basic science related to diabetes	60	39
among these on receptors	13	
on immunology	3	
Transplantation of beta cells	12	8
Pathophysiology of diabetes	41	26
among these, on exercise	7	
Surveys, genetics, epidemiology	5	3
Therapy	5	3
among these, on oral agents	1	
Nutrition	4	3
Patient education	3	2
Pumps, CSII	2	1
Complications	15	15
among these, on eyes	7	
cardiovascular	7	
nerve	1	
Pregnancy	1	0
Psychosocial aspects	2	1
Obesity	5	3

Obviously some areas are better represented than others. The distribution reflects past training along traditional lines which was often of very high quality. There is considerable strength in some areas of basic research, e.g. G.I. peptides, glucoregulation, receptors and exercise; other areas are not as well represented. Most conspicuous among the latter are epidemiology, genetics and research on oral agents and nutrition.

2. Manpower

We have attempted to assess the resources needed to maintain the current national effort in diabetes research. The analysis can be extended to account for any increase in this effort which seems desirable.

According to the report of the Diabetes Canada Research Advisory Committee submitted to Diabetes Canada and the Medical Research Council of Canada in 1984, 112 researchers were active in research dealing with diabetes or some closely related project. In the following we attempt to analyze the requirements and costs of a training program needed to maintain this number.

(a) How many trainees should complete research training per year? If the average productive period of the presently active researcher is taken as 10 years then the estimated number of trainees needed is calculated as 112/10, or 11 per annum. If the total number of researchers were to be increased by the training program then the annual requirements for trainees should be multiplied by the ratio of the desired number over 100. Of course it is possible that the number of researchers may be increased by training Canadian candidates elsewhere or inviting researchers from other countries to settle in Canada.

(b) What is the number of trainees in the program in any given year? To estimate the number of active trainees the length of the training period has to be known. We have estimated this to be 6 years for a basic scientist. This is calculated as the sum of 4 years of training for the Ph.D. degree plus 2 years of Post Doctoral Fellowship (PDF). For a medical graduate to obtain a Ph.D. is expected to take 4 years on the average. For a clinical researcher the specific training period, in addition to the traditional residency training requirements, is estimated to be 4 years: one year of residency taken as an option in research plus 3 years as a Ph.D. and/or Clinical Fellow. The number of trainees in the programs thus will vary according to the ratio of science-based and clinical-based trainees.

The Advisory Group found that in 1983 44% of the trainees were in the basic sciences, 56% in clinical research. If this ratio were maintained the number of trainees in the system needed to produce 11 "graduates" per year (i.e. the maintenance requirements) would be 52[1]. This estimate assumes that all candidates complete their training and are successful in receiving operating grants for their research.

(c) What are the more realistic requirements considering the proportion of trainees who obtain grant support? It is highly improbably that all who finish research training will embark on a research career in diabetes. The number may be reduced by a change in the field of interest or in career plans (e.g.

switching to clinical work) perhaps necessitated by not being able to find support for research in the form of a grant or contract.

Assuming that all trainees eventually seek grant support for diabetes research how many actually achieve grant support? The Medical Research Council statistics indicate that about 30% of new applicants for grant support are successful. This would be a worst case estimate which assumes that each trainee will apply no more than once (i.e. will be "turned off" by a single failure to gain support). Multiple applications are the rule however and the ultimate success rate is not readily predictable. Assuming an 80% success rate, then the number of trainees in the system necessary to maintain the status quo would be 52 ÷ 0.8 = 65.

(Alternatively if the success rate were 50% or 40% the corresponding trainee numbers would be 104 (52 ÷ 0.5) and 130 (52 ÷ 0.4)).

(d) How much money is required to maintain the status quo? Given the above considerations and the current graduate student and postdoctoral stipends (i.e. graduate student, $11,000/yr.; Ph.D. postdoctoral, $20,000/yr.; M.D. training fellowship after internship, $30,000/yr.) we can estimate the annual cost of a maintenance program. From the stipends and our estimates of average training duration the average annual stipend of a science-based candidate is $14,600 while that for an M.D. is $30,000. If the current mix of science and clinically-based trainees (i.e. 44 : 56) is maintained the cost per candidate per yr. is $23,231.00. Thus the annual cost to maintain a program of 65 candidates would be $1,510,000. It is realistic to consider that training laboratories receive funds to cover training costs for each postdoctoral trainee. In the United States this research allowance is approximately 20% of a postdoctoral stipend.

We emphasize that the above results are contingent on the specific assumptions stated[1] and refer to a status quo situation in which there is no expansion of the total number of diabetes researchers via Canadian training grants and programs. It is also assumed that the number of Canadian trainees lost via recruitment to centres outside of Canada will approximate the number of foreigners recruited to Canadian institutions.

(e) What happens after training? In the steady-state situation there should be a regular supply of available positions as a consequence of normal turnover. If it is decided to expand the overall pool of Canadian diabetes researchers then suitable positions must be available at universities, and hospitals, as well as in government and industrial laboratories. If the training programs are doing a good job they will carefully select their candidates and provide quality training so that trainees will have a better than average chance to be successful in scholarship and grant competitions. If Diabetes

Canada were to offer Career Development Awards, in a manner analogous to the National Cancer Institute or Ontario Heart Foundation, this would help secure the future careers of suitable trainees.

3. How is the Present Situation Perceived by Researchers?

In an effort to obtain some idea of how clinicians and researchers in Canada feel about the state of diabetes research in this country a short questionnaire was circulated. There were 18 respondents and the major problems identified were: (1) an insufficient number of well-trained investigators; (2) inadequate funding of operating grants; and (3) inadequate support for epidemiologic research. The respondents felt that the funding agencies should place high priority on correcting these deficiencies, and that there should be an effort to coordinate funding between the MRC and the voluntary organizations.

These views correspond with the general recommendations made in Nov. 1984 by "The Joint Task Force on Clinician-Scientists" and with the recent report of the "Diabetes Canada Research Advisory Committee". The key recommendations of: "The Joint Task Force" aimed at increasing funding for personnel engaged in research may be abbreviated as follows:

1. Assess the efficacy of summer studentship awards in influencing research career choices.
2. Maintain post-MD fellowship awards as a high priority while assessing the extent to which recipients end up pursuing research careers.
3. Establish a transition award similar to the New Investigator Research Award (NIRA) or the Clinical Investigator Award (CIA) provided by the NIH to foster the careers of clinician-scientists.
4. Establish selective training grant programs.
5. Recommend to the Royal College of Physicians and Surgeons to allow more flexibility to research trainees preparing for fellowship accreditation.

GENERAL PERSPECTIVE ON POLICY

Should some areas of research be given priority in funding and/or training grants? Should"envelopes" of funds be designated for these areas? However carefully considered, such designation of priorities always carries an element of arbitrariness. Forcing the diversion of funds to such designated areas may lead to the abandonment of productive projects in some disfavoured areas of research. Should the value of such projects be realized at a later date, their resuscitation would be both expensive and time-consuming. Moreover designation of such areas might attract investigators who have not been able to find success in other competitions.

To strengthen the national effort in diabetes research two pathways seem to be open. They are not mutually exclusive and indeed could be pursued in parallel.

1. "Support excellent programmes". Support those existing diabetes related projects that are productive, both with operating and training grants irrespective of the field of interest. This approach is likely to produce good quality research, but as the only policy to be followed would be too narrow and conservative.

2. "Open up new areas of excellence" by:

   (a) Training young investigators in such newly developing research areas outside Canada. Since fellowships should be allocated on the basis of the candidate's capabilities and not primarily on the designation of a special field of interest, the pitfalls mentioned above would be avoided.

   (b) Re-direct already existing, proven expertise to diabetes related research; e.g. researchers with accomplishments in molecular biology may receive grants related to biotechnology of peptide hormones or the genetics of diabetes; or epidemiologists may undertake surveys of national interest, etc.

The success of both approaches depends on both adequate and stable funding. Without this any policy initiative will be unsuccessful.

Specific Recommendations

Given the current situation in Canada and the general perspective outlined above we recommend in order of priority that:

1. A suitable subcommittee should be established to analyse the implications and means for implementing the following policies.

2. Training grants from new sources provided by government should be made available to suitable programs which can then recruit potential trainees in a more assured manner. Such an approach may reduce the likelihood that fine Canadian candidates are lured away to greater opportunities elsewhere. The program should be awarded in open competition and reviewed periodically with respect to both the program and trainees. It is expected that the trainees would compare favorably to those receiving individual fellowship support, and would be at least comparably successful in launching investigative careers. The training program mechanism is the major mechanism operative in the U.S. for the support of diabetes research trainees (i.e. in 1983 80% of trainees were supported via training grants).

3. Diabetes Canada should direct a substantial portion of the funds raised to the support of clinical scholarship awards analogous to MRC scholarships, in order to meet the recognized need for more researchers in diabetes.

4. The RCPS(C) should reduce the amount of clinical training deemed necessary for speciality certification so as to permit trainees to pursue research endeavours in the area of diabetes.

5. The base salary of established clinician scientists should be sufficient to allow them to maximize their research time.

6. The issue of coordinating funding between the MRC and voluntary fundraising organizations (viz. CDA and JDF) should be addressed.

FOOTNOTES

1. To calculate the total number of trainees in the system we have assumed that: (a) the duration of training for a Ph.D. = 6 years and that for an M.D. = 4 years; (b) the proportion of Ph.D. to M.D. trainees is 44 : 56.

Now let the total number of trainees = z
If the number of M.D.'s each year = x
and the number of Ph.D's in each year = y

then $x + y = 11$ [annual replacement rate]
and $6(x) + 4(y) = z$ [assumption (a)]
However $0.44z = 6x$
and $0.56x = 4y$

Now we solve for x and y in terms of z

$$x = \frac{0.44z}{6}$$

and $$y = \frac{0.56z}{4}$$

Substituting into the above we see that

$$\frac{0.44z}{6} + \frac{0.56z}{4} = 11$$

Solving we find $z = 51.6$ or 52

Reference

1. The Diabetes Canada Research Advisory Committee: Diabetes Related Research in Canada. Can Med Assoc J 1985; 133:103-105.

COMMENTS AND SUMMARY OF THE MEDICAL RESEARCH COUNCIL AND ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA JOINT TASK FORCE REPORT ON CLINICIAN SCIENTISTS IN CANADA

R. Marvin Bala, M.D.

The Task Force on Clinician Scientists in Canada was jointly established by the Medical Research Council of Canada and the Royal College of Physicians and Surgeons of Canada. The terms of reference for the Task Force included:

1. To make definite proposals to the sponsoring bodies on methods for promoting the entry into research, the research training and research career opportunities for clinician scientists, taking into account the recommendations of the M.R.C.-R.C.P.S.C. Committee on the clinician scientists in Canada (June, 1981) and the Report of the Task Force to study the application of biomedical research to health care (December, 1980).
2. To examine how the programs of M.R.C. and R.C.P.S.C. could be adjusted to support the training of clinician scientists.

The Task Force concluded that these terms of reference indicated that the M.R.C. and the R.C.P.S.C. had concluded that the number of clinician scientists in Canada was less than desirable and modifications were required in the respective programs to enable Canadian clinician scientists to play an increased role in overall medical research. The Task Force therefore accepted the previous reports and proceeded from there. The Task Force interviewed various directors of programs and individual clinician scientists to obtain representative views. It was generally agreed that there was need for more clinician scientists to participate in medical research in Canada. The clinician scientist was defined as an M.D. who participated in medical research and was active in patient care. The subsequent recommendations of the Task Force focussed on methods to increase the numbers of clinician scientists, methods to increase the duration of their active participation in medical research and mechanisms by which the clinician scientists' productivity in medical research could be increased.

The Task Force report emphasized the recent increasing importance of the clinician scientist who may primarily carry out clinical research requiring in depth expertise in epidemiology and biostatistics and a rigorous methodologic approach in addition to the clinician scientist who undertakes bench type research. The Task Force report underlines the increasing complexity of medical research and competitiveness for limited funding. Both of these factors often discourage the clinician from medical research or result in early abandonment of this commitment. The relative decline in university budgets has resulted in financial stresses on the geographic full-time appointees who have high demands for clinical service and are required to generate large proportions of their salaries from patient care while carrying out academic activities related to teaching and medical research. The academic survival of clinician scientists in this milieu has become increasingly difficult without adequate protected time for medical research. This is mostly apparent in those medical schools in which the academic leadership does not strongly support medical research or does so through lip service rather than substance and example.

The following will summarize the recommendations of the Task Force:

1. "That the A.C.M.C. be encouraged to repeat the type of survey carried out in 1978-79 to document contemporary attitudes of medical students to research. Such a project should qualify for Federal Government support."
   The above previous A.C.M.C. study revealed that approproximately 5% of students were definitely interested in a medical research career and another 15% could be interested. During the medical curriculum a similar number seemed to change away from or toward an interest in medical research. The primary reason for lack of interest in medical research was the sense of insecurity within a medical research career and the occasional lack of apparent relevance of bench type medical research to patient care. As additional factors have emerged since that A.C.M.C. study, in particular the development of the epidemiological and biostatistical approach to clinical research, the Task Force felt that this study should be repeated to provide more contemporary information related to medical student interest in a career which includes medical research.
2. "That the M.R.C. obtain data about the administration of summer studentship awards, including criteria for selection of candidates and supervisors and the subsequent careers of awardees. This study should be designed and supervised by the M.R.C. Standing Committee on Manpower and could provide criteria for future funding of the program."
   M.R.C. assigns a high importance to summer studentship support through awards to Deans of Medical Schools. M.R.C. however has little data of the success of this program and exercises little control over the award process which is variably administered and appears to be variably successful at the various medical schools.
3. "That the University of Manitoba be encouraged to evaluate the impact of their B.Sc. (Med) program upon undergraduates and faculty. Should such a report provide convincing evidence of the program's efficacy, M.R.C. might encourage and assist other schools to institute similar programs."
   The Manitoba B.Sc. (Med) program through summer studentships has been highly successful in the past in developing clinician scientists who have assumed productive medical research roles as well as medical research leadership in Canada. The Task Force felt that further data and an update would be useful for potential future recommendations. The Task Force did not carry out a detailed analysis of the combined M.D./Ph.D. training programs. In general the Task Force recommended that the usual training should be M.D. followed by clinical specialty training and then by research training.

4. "That post-M.D. fellowships for research training remain a high priority for the Council".
The M.R.C. fellowships are the major funding source for training medical scientists in Canada. The Task Force supported separate M.R.C. committees and competition for fellowships by the M.D./D.D.S./D.V.M. versus the Ph.D. applicants for fellowships. These two groups have similar numbers of applications and awards of fellowship. The number of applicants for fellowships have approximately doubled during the last decade; however, the number of fellowship awards has not increased so that relatively fewer applicants are successful in obtaining fellowship awards (50% versus 90% previously).

5. "That M.R.C. assess the efficacy of the current Fellowship program through a study including such factors as selection criteria and subsequent careers of fellows".
The Task Force believed it was important to follow up subsequent medical research commitment and productivity of those supported in the fellowship program. Of the M.R.C. Fellows in 1973 approximately 40% of the M.D. and 70% of the Ph.D. Fellows held research grants five years later. Over the last decade the number of applications for M.R.C. Scholarships from Ph.D. candidates is gradually increasing so that in 1983 these were more than double that from M.D./D.D.S./D.V.M. candidates.

6. "That M.R.C. consider establishing a training grant program for clinician scientists, the detailed mechanisms of such a program to be determined on the recommendations of the Standing Committee on Manpower".
The Task Force believed that training grants would offer stability to excellent training programs and would allow development of increasing numbers of medical researchers in focus areas. The Task Force believed that these training grants could be modelled on the dental and biotechnology training grant programs.

7. "That Council establish a Clinician Scientist Training and Establishment Award to include salary support for Fellowship training and initial appointment to faculty. Such awards would ordinarily extend for a five-year period (3 years training, 2 years faculty establishment) and provide operating funds at the time of the faculty appointment".
Limited university budgets often preclude appointment guarantee for excellent trainees and results in a feeling of insecurity. The award of an M.R.C. scholar type salary and an establishment operating grant for 2-3 years of the initial faculty appointment to those who are successfully completing an M.R.C. Fellowship training program would lead to greater stability and development of competitiveness in regular applications by the new appointee.

8. "That the President of M.R.C., taking such ad hoc committee or other advice as he deems necessary, evaluate new and innovative proposals in the area of developmental technology and support those deemed worthy".
The Task Force believed that there should be some mechanism to support innovative research, particularly that involving

developmental technology, related to diagnosis and therapy carried out by some clinician scientists in fields such as surgery and radiology.

9. "That one or more individual(s) with clinical research experience be recruited for a suitable staff position(s) at M.R.C.".
The Task Force recognized that members of the M.R.C. staff were commonly unfamiliar with the fundamental aspects of clinical training and the working requirements of clinical investigators.

The Task Force then came out with a number of recommendations directed to the Royal College of Physicians and Surgeons of Canada. The Research Committee of the Royal College considered these recommendations and either endorsed these or suggested modifications. The Task Force recognized that the Royal College supported the concept of medical research training for different periods of time in the various specialty training programs. However, there were no mechanisms to ensure that this occurred, nor was it ensured that research opportunity was available within these programs. The Task Force additionally noted the recent trends of various Royal College subspecialty training programs to increase the number of clinical training years required to meet certification standards. The Task Force did not support the latter trend as this would significantly increase the overall training time required by the clinician scientist to obtain the clinical certification and an adequate research training. The Task Force believed that there should be an opportunity to pursue research options within the residency years in all programs of the Royal College.

This resulted in the following Task Force recommendation:

10. "That the R.C.P.S.C. make accreditation of specialty and subspecialty training programs conditional on a satisfactory level of research by faculty identified with the program".
The Research Committee of the Royal College supported this recommendation and added the following recommendation "That within five years or by the time of the next Royal College survey, whichever is longest, full approval of programs will require a satisfactory level of research".

11. "That the R.C.P.S.C. discourage trends that increase the number of years of clinical training necessary for specialty certification at the expense of optimal years for research".
This was supported by the Royal College Medical Research Committee.

12. "That a year of research be an optional but creditable year toward requirements for certification in all primary specialties of the College".
This was supported by the Royal College Committee on Medical Research.

13. "That a year of research be an optional but creditable year toward requirements for Certificates of Special Competence, and for specialties recognized in the future by the R.C.P.S.C.".
The Royal College Research Committee supported this recommendation and further emphasized concern that it was possible to complete all

training in the primary specialty and subsequent subspecialty with no research experience whatsoever in present Royal College programs. This committee believed that the various subspecialties were on the forefront of medical research and had potential for major contributions by clinician scientists.

14. "That the R.C.P.S.C. encourage the opportunity for well supervised research in an increasing number of specialty training programs".
The Royal College Research Committee supported this recommendation and added the following "An integral part of residency training should be the completion of a clinical research project".

15. "That the R.C.P.S.C. consider that exceptional candidates, on the recommendation of the Chairman of the department, be permitted primary certification with two rather than three core years in order to allow up to two years of research in the normal five year program for primary and special competence certificates".
The Task Force noted that this was similar to a previous recommendation from the Canadian Chairmen of the Departments of Medicine and that this was not accepted by the Royal College. The Royal College Research Committee fully supported this recommendation and recommended its reconsideration by the Royal College Council.
The Royal College Research Committee expressed further concern that research training cannot be carried out as part of the residency training program due to certain restrictions in this regard in some provinces. The Royal College committee therefore drafted this further recommendation:
"That the College inform provincial ministries which fund residents and post-graduate committees of the medical schools, that it considers all of its training requirements, optional or compulsory, as valid and important in the training of specialists and that it is opposed to policies that would exclude or discriminate against some training requirements, such as research, on the basis of non-funding".
The Royal College Research Committee further recommended that the Royal College re-evaluate the success of its Research Professorship Program.

The joint Task Force report and the additional recommendations by the Research Committee of the Royal College are being considered in detail by the Councils of both the M.R.C. and the Royal College.

ROLE OF A
NATIONAL TASK FORCE

THE ROLE OF A NATIONAL DIABETES TASK FORCE: SOME LESSONS FROM THE PAST.

Oscar B. Crofford, M.D.

In 1974, the Congress of the United States passed the National Diabetes Mellitus Research and Education Act (Public Law 93-354). Although this law ultimately proved to have a significant impact on the National Institutes of Health (NIH), it is noteworthy that it did not originate within NIH. Indeed, it was opposed in congressional testimony by witnesses from the Department of Health, Education and Welfare. It would be more accurate to say that the National Diabetes Mellitus Research and Education Act had its beginnings with citizens who represented the deeply concerned parents of children with diabetes such as Mrs. Lee Ducat of Philadelphia, founder and first president of the Juvenile Diabetes Foundation, and Mrs. Harris J. (Joyce) Kortman from Holland, Michigan, and Mr. Carol Stengler of Pennsylvania. Physicians who made important contributions during those early years were Drs. John K. Davidson from Atlanta and the late Robert H. Williams from Seattle. A number of congressional leaders were especially responsive, most notably Senator Richard Schweiker of Pennsylvania and the late Senator Gail McGee, himself a diabetic, Congressman Guy Vander Jagt of Michigan and the late Congressman William Steiger, also a diabetic. A more complete description of the history of Public Law 93-354 was written by Dr. John K. Davidson and published by the American Diabetes Association in "Forecast" (1).

One of the provisions of the "Diabetes Law" was the establishment of a National Commission on Diabetes whose charge was to develop a long-range plan that would lead to a more comprehensive, more sustained and better coordinated effort in dealing with the problems and frustrations confronting persons with diabetes and their families. The Commission was given a number of important authorities. These included the authority to appoint its own staff, to hold public hearings, to obtain outside consultants and, more importantly, to deliver its report to Congress without prior administrative approval. A budget of one million dollars ($1,000,000.) was authorized, and the Commission was given nine months to complete its report. The makeup of the Commission included seven directors of key NIH institutes, four members of the general public, two of whom should have diabetes or be parents of children with diabetes and six physician/scientists including Drs. George Cahill and Paul Lacy. The Commission was authorized to select its own chairman and I was elected as a "compromise candidate". At that time, there was substantial tension between the Juvenile Diabetes Foundation and the American Diabetes Association and Dr. Cahill, the natural choice for chairman of the Commission, was soon to be the president of the American Diabetes Association. I resigned as a member of the ADA's Board of Directors and attempted to encourage the commission to function as harmoniously as possible. Dr. Keatha K. Krueger was the Executive Secretary to the Commission and my closest working associate.

Other important authorities given to the National Commission on Diabetes included the authority to recommend budgets for each of the key NIH institutes; budgets that were sufficient to provide adequate funding for the programs to be included in the long-range plan. It was also noteworthy that while the law directed the NIH to establish Diabetes Research and Training Centers and authorized an appropriation for this process, the law stated that the Diabetes Research and Training Centers should be established in a manner that was "consistent with the applicable recommendations" of the Commission. In summary, I think it is fair to say that there have been no categorical disease laws passed since that time that gave to an independent commission authorities that were as broad as those granted to the National Commission on Diabetes.

The Commission met for the first time in March of 1975 and initiated a series of deliberations aimed at preparing a report for submission to Congress by December. Four principle committees were established and each committee formed a series of work groups. Nearly 300 experts in diabetes and diabetes-related disciplines from the United States, Canada and Western Europe were involved, and the commission heard extensive public testimony in cities throughout the nation. There were few, if any, scientists who did not have the opportunity to serve on a work group that was relevant to their interests and there were many opportunities for individuals with diabetes to present testimony before the commission either in person or in writing. This was the first time in our history that we had ever had a comprehensive "Diabetes Law" and enthusiasm and support for the activities of the Commission were high. Drs. George Cahill and Paul Lacy were very instrumental in setting up the scientific work groups and there was not a single individual who was invited to serve who declined.

The Long-Range Plan to Combat Diabetes was delivered to both houses of Congress on December 10, 1975 and Volume I of the report was published by the American Diabetes Association in a special edition of "Forecast". The preface stated that "the long-range plan was developed on the basis of information collected in a comprehensive survey of the epidemiology and nature of diabetes and its economic and social consequences...The result was the formulation of a plan that represents the expressed needs of an interacting social system - the patient, the health care deliverer, the medical researcher, and the public".

The Long-Range Plan to Combat Diabetes consisted of four major components: (1) Diabetes Research Programs, (2) Diabetes Research and Training Centers, (3) Diabetes Health Care, Education and Control Program Activities, and (4) the National Diabetes Advisory Board.

Important elements of the plan were that the recommendations were made as specific as possible and that each recommendation was directed to a specific agency. For example, in the area of personnel training the following recommendation is taken directly from the Commission report: "The National Commission on Diabetes recommends to the National Institute of Arthritis, Metabolism and Digestive Diseases, the National

Eye Institute, the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute of Dental Research, and the National Institute of Child Health and Human Development that they make every effort to expand the fellowships and special awards in the area of diabetes-related studies in accordance with the levels indicated". This was followed by a table that recommended the exact number of Fellowship positions, Research Career Development awards and Distinguished Scientists awards for each of the five institutes mentioned and for fiscal years 1975 through 1980. The importance of specific recommendations cannot be overemphasized for it served as a yardstick to assess the performance of each and every Institute regarding their part in implementation of the Long-Range Plan.

Let me cite another example. "The National Commission on Diabetes recommends that the National Heart and Lung Institute and the National Institute for Arthritis, Metabolism and Digestive Diseases initiate and support a five-year clinical study to assess the effect of treatment of juvenile onset diabetes on the development of microvascular and macrovascular complications". This recommendation, and its eventual acceptance by the Congress, has provided the legislative underpinning for the Diabetes Control and Complications Trial that is now operative.

Other specific recommendations that have been implemented were recommendations for the establishment of the National Diabetes Information Clearing-house, recommendations for establishment of the National Diabetes Data Group, and recommendations that the Diabetes Control Program activities be established by the Secretary using the framework of the Center for Disease Control. The Commission's recommendations for the Diabetes Research and Training Centers were developed in great detail and it ultimately proved to be extremely important that the law specified that the DRTC administrative guidelines be "consistent with applicable recommendations of the National Diabetes Commission."

A final and most important element of the Commission report was the establishment by law of the National Diabetes Advisory Board. During the nine months of deliberations, it had become apparent that the NIH would probably resist with great vigor the highly specific nature of the Commission's report. It was unprecedented that Institute budgets would be recommended directly to the Congress and bypass the customary budgeting process that the NIH employed and that came under the careful scrutiny of the Secretary for Health, Education and Welfare. The Commission had the strong feeling that its report was a good one and believed that its task would not be complete without establishing a mechanism to oversee the implementation of the Long-Range Plan. We, therefore, recommended the establishment of a National Diabetes Advisory Board to oversee the implementation of the plan, to modify and update the plan as necessary and to report annually to Congress the progress made by each federal agency. We obtained private legal counsel to draft the appropriate legislation which eventually became law. This aspect of the Commission report has remained highly controversial but, despite this controversy, authorization for the National Diabetes Advisory Board has been maintained and nine new members were appointed quite recently. The Board has been very effective in its work and many members of the diabetes community (physicians, individuals with diabetes, parents of children with diabetes, nurses, and other concerned individuals) have had the opportunity to serve.

The budgetary recommendations of the National Commission on Diabetes were projected forward for five years and were given serious consideration by the Appropriations Committees of the Congress. Funds for the support of diabetes research increased at an unprecedented rate in the years immediately following the Commission report. Although the rate of increase at the present time is generally comparable to that of NIH as a whole, the establishment of a new funding base has resulted in the fact that the diabetes programs are probably more generously funded than those of most other categorical diseases. With our political system, one cannot underestimate the importance of establishing a new base level of funding, since funding increments in subsequent years will rarely, if ever, be below those of NIH as a whole.

In summary, we will probably never have another National Commission on Diabetes in the United States. It is exceedingly difficult, if not impossible, to establish categorical disease commissions at the present time. Following the model of the National Commission on Diabetes, we have seen an arthritis commission, a digestive disease commission and, I believe, even a kidney commission. All of these have developed reports which were quite similar to that of the National Commission on Diabetes, including the establishment of their own oversight advisory boards. The success of the Diabetes Commission in establishing new diabetes programs that have all resulted in increased federal expenditures related to diabetes is inconsistent with current trends to reduce federal spending on every front. In a sense, one could argue that the National Commission on Diabetes and the implementation of its report were "too successful" in the minds of our present administration (3). Hopefully, the timing is such that the National Diabetes Task Force in Canada will also be successful. Perhaps some aspects of the history of a similar effort in the United States will prove to be applicable.

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GLOSSARY OF TERMS

GLOSSARY

AADE: American Association of Diabetes Educators.

Abetalipoproteinemia: a hereditary syndrome, transmitted as an autosomal recessive trait, characterized by a lack of B-lipoproteins in the blood, acanthocytosis, hypocholesterolemia, progressive ataxic neuropathy, atypical retinitis pigmentosa with involvement of the macula, and malabsorption.

Ablation: 1. separation or detachment, extirpation, eradication 2. removal of a part, especially by cutting.

Abscissa: one of two coordinates, the other of which is called ordinate, used as a frame of reference. The abscissa is usually horizontal and the ordinate vertical and, when suitable values have been assigned to them, corresponding data can be plotted.

Acetylator: a cofactor with a high acetyl group transfer potential, which required in many enzyme catalyzed acetylations.

Acromegaly: a condition caused by hypersecretion of the pituitary growth hormone after maturity and characterized by enlargement of extremities of the skeleton - the nose, jaws, fingers, and toes.

ADA: American Diabetes Association

Adipocytes: fat cells.

Aerosolized: a solution, which has been atomized into a fine mist; used for inhalation therapy.

Agonist: acting in the same direction; having the same effect.

Albuminuria: presence in the urine of serum albumin.

Albustix positive proteinuria: detection of protein in the urine using the reagent strip called Albustix.

Aldose reductase inhibitor: an inhibitor of the enzyme aldose reductase which converts glucose into sorbitol.

Alleles: one of two or more alternative forms of a gene occupying corresponding sites on homologous chromosomes, any two of which may be carried by a given individual and which determine alternative characters in inheritance.

Allergenic: acting as an allergen; inducing allergy.

Allograft: a graft of tissue between individuals of the same species, but of disparate genotype; called also allogenic graft and homograft.

Aminoacid: an acid with a monovalent chemical group; the smallest part of a protein.

Amitriptyline: amitriptyline hydrochloride: a white or almost white, odorless, crystalline powder or small crystals, soluble in water, alcohol, chloroform, and methanol; used as an antidepressant.

Amniocentesis: surgical transabdominal perforation of the uterus, to obtain amniotic fluid.

Amyotrophic: pertaining to the progressive weakening and wasting of muscles accompanied by an aching or stabbing pain, usually limited to the muscles of the pelvic girdle and thigh, and, rarely, associated with diabetes.

Anabolism: any constructive process by which simple substances are converted by living cells into more complex compounds, especially into living matter.

Analogue: chemical compounds with a structure similar to that of others but differing from them in respect to a certain component; they may have a similar or opposite action metabolically.

Angina: spasmodic, choking, or suffocative pain; now used almost exclusively to denote angina pectoris.

Antibiotic: a chemical substance produced by a micro-organism which has the capacity, in dilute solutions, to inhibit the growth of, or to kill, other micro-organisms.

Antigenicity: potency as an antigen.

Antigen: any substance which is capable, under appropriate conditions of inducing the formation of antibodies and of reacting specifically in some detectable manner with the antibodies so induced.

Anti-insulin antibody: a substance that counteracts the action of insulin.

ApoAI, ApoB, ApoCII, ApoCIII, ApoE: these are all types of protein to which triglyceride and cholesterol are linked for transportation in the circulation.

Apolipoprotein: the protein moiety (moieties) of plasma liproproteins which binds the lipid moiety to form the holoprotein.

Argon: a chemical element, atomic number 18, discovered in the atmosphere in 1895. One of the inert gases.

Arteriolar: pertaining to or ressembling arterioles.

Arterioles: a minute arterial branch, especially one just proximal to a capillary.

Artificial beta cell: artificial pancreas.

Atelia: imperfect or incomplete development.

Ateliotic: pertaining to or characterized by atelia.

Atherogenesis: the formation of atheromatous lesions in the arterial intima.

Atheromata: a mass of plaque of degenerated, thickened arterial intima occuring in atherosclerosis.

Atherosclerosis: an extremely common form of arteriosclerosis in which deposits of yellowish plaques (atheromas) containing cholesterol, lipoid material, and lipophages are formed within the intima and inner media of large and medium-sized arteries.

Atony: lack of normal tone or strength.

Autoimmunity: a condition characterized by a specific humoral or cell-mediated immune response against the constituents of the body's own tissues (autoantigens); it may result in hypersensitivity reactions or, if severe, in autoimmune disease.

Axon: that process of a nerve cell by which impulses travel away from the cell body; called also axis cylinder.

Axonal: pertaining to or affecting an axon.

Axotomy: the transection of an axon.

Bacteriostasis: the inhibition of growth, but not the killing, of bacteria by chemicals or biologic materials.

Basal insulin secretory rate: the continuous release of insulin from the pancreas which is independent of food ingestion.

BB rat: a special species of rat with a high genetic predisposition to develop insulin dependent diabetes.

BMT: basement membrane thickness.

B- cells: the beta cells of the pancreas which synthesize and secrete insulin.

Beta VLDL: an abnormal, very low density, lipoprotein.

Biguanides: a class of oral hypoglycemic.

Biosynthesis: pertaining to or characterized by biosynthesis; the synthesis of a product by a living organism.

BHI: biosynthetic human insulin.

Bioavailability: the degree to which a drug or other substance becomes available to the target tissue after administration.

Biochemical: pertaining to biochemistry.

Biothesiometer: an instrument for measuring the vibratory-perception threshold.

Bolus: is said of an insulin dose given all at once in a single injection, particularly before meals.

Bovine, BI: insulin derived from the ox (cattle).

Bowman's capsule: the capsula glomeruli; the capsule of the glomeruli (functional unit) of the kidney.

BP: Blood pressure.

Brittle diabetes: diabetes which is very difficult to control and characterized by wide variations of blood glucose.

Buffer: a chemical system that prevents change in the concentration of another chemical substance, e.g. the proton donor and acceptor systems serve as buffers preventing marked changes in hydrogenions concentration.

Cachexia: a profound and marked state of constitutional disorder; general ill health and malnutrition.

C.D.A.: Canadian Diabetes Association.

Calisthenics: a system of light gymnastics for promoting strength and grace of carriage.

Cannula: a tube for insertion into a duct or cavity; during insertion its lumen is usually occupied by a trocar.

Carbamazepine: a crystal compound, used as an anti-convulsant and analgesic.

Cellulitis: inflammation of cellular tissue; especially purulent inflammation of the loose subcutaneous tissue.

CHO: carbohydrates.

Chlorpropamide: an oral hypoglycemic agent of the sulfonylurea family.

Cholesterol: a pearly, fatlike monatomic alcohol crystallizing the form of leaflets or plates from dilute alcohol, and found in animal fats and oils, in bile, blood, brain tissue, milk, yolk of egg, myelin sheaths of nerve fibres, the liver, kidneys, and adrenal glands. It constitutes a large part of the most frequently occurring type of gallstones and occurs in atheroma of the arteries, in various cysts, and in carcinomatous tissue.

Chylomicron: a stable droplet containing 86 percent triglyceride fat, 3 percent cholesterol, 9 percent phospholipids, and 2 per cent protein, found in the intestinal lymphatics (lacteals) and blood during and after meals; this is the form in which absorbed long-chain fats and cholesterol are transported from the intestine.

CIA: Clinical Investigator Award

Clones of E coli: a strain of E. coli derived from a single microorganism.

Compromised beta cell reserve: limited capacity of the pancreatic beta cells to synthesize and release insulin.

Contaminating antigen: substance capable of inducing antibody and consequently allergic reaction.

Continuous subcutaneous insulin infusion: the continuous infusion of insulin with a pump.

Coxsackie B4: a group of enteroviruses producing in mass a disease resembling poliomyelitis but without paralysis.

Connecting peptide (C-peptide): a small protein which is part of the proinsulin molecule connecting the alpha and beta chain of the insulin molecule. The C-peptide is cleaved off within the pancreatic cells and is released into the circulation with insulin.

C-peptide activity: measurable C-peptide immunoreactivity in the plasma or urine.

Creatinine: a basic substance, creatine anhydride which is filtered by the kidney and excreted in the urine; can be used to measure glomerular filtration rate.

CSII: continuous subcutaneous insulin infusion

CVD: color-vision - deviant (showing anomalies of color vision), or color vision deviate (an individual showing anomalies of color vision.

Cyclandelate: a white to pale yellow crystalline powder, soluble in alcohol, used as a vasodilator in peripheral vascular disease.

Cyclooxygenase: enzyme that catalyzes the incorporation of oxygen into a substrate.

Cyclosporin: an immunosuppressant drug, which is used to prevent rejection of transplanted organs.

Cystometry: the study of bladder efficiency by means of the cystometer.

Cytolysis: the dissolution or destruction of cells.

Cytolytic: pertaining to, characterized by, or causing cytolysis.

DCCT: Diabetes Control and Complications Trial (U.S. National Institute of Health sponsored)

DCV: distribution of conduction velocity.

Decamethylenediguanidine: a compound used in the treatment of myasthenia gravis.

Degraded insulin (desamido-and arginyl-insulin): insulin that has been degraded to other compounds of different activity.

Demyelination: the destruction or removal of the myelin sheath of a nerve or nerves.

Denervation: resection, or removal, of the nerves to an organ or part.

Dephosphorylation: removal of the trivalent PO_3 group from organic molecules.

Dermal nerve: nerve innervating the skin.

Diabetes Canada: a joint project of the Canadian Diabetes Association, the Quebec Diabetes Association and the Juvenile Diabetes Foundation to raise money for diabetes research from the national corporations.

Diabetic BB - Wistar Rat: see BB rat.

Diabetic glomerulosclerosis: specific lesions of the kidney due to longstanding poorly controlled diabetes.

Diabetic ketoacidosis: a complication of diabetes due to insulin deficiency resulting in production of ketone bodies and acidoses; if not corrected by insulin administration it can lead to coma and death.

Diabetogenic: having the capacity to produce diabetes.

Diabetologist: a physician with special expertise in the treatment of diabetes.

Diphenylhydantoin: a white odorless powder, used as an anticonvulsant in grand mal epilepsy.

Distal: remote; farther from any point of reference; opposed to proximal.

Distal femoral epiphysis: the distal end of the femur.

Dizygotic: pertaining to or derived from two separate zygotes, as dizygotic (fraternal) twins.

DKA: diabetic ketoacidosis.

DMES: Diabetic Macular Edema Study.

DNA: deoxyribonucleic acid.

Doppler velocimetry: measurement of blood flow using the doppler.

DRS: Diabetic Retinopathy Study.

DRTC: Diabetes Research and Training Centers

DRVS: Diabetic Retinopathy Vitrectomy Study.

DVM: Doctor of Veterinary Medicine.

Dyslipoproteinemia: abnormal lipoprotein in the circulation.

Edema: the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body; usually applied to demonstrate accumulation of excessive fluid in the subcutaneous tissues.

Electromyography: the recording and study of the intrisic electrical properties of skeletal muscle and nerves.

ELISA: enzyme linked immunosorbant assay for determination of micro-quantities of albumin in the urine.

Endocrinology: the study of the endocrine system and its role in the physiology of the body.

Endogenous: 1. growing from within. 2. developing or originating within the organism, or arising from causes within the organism.

Endoneurial: pertaining to the endoneurium.

Endothelial (pericytes): pertaining to or made up of endothelium.

Endothelium: the layer of epithelial cells that lines the cavities of the heart and of the blood and lymph vessels, and the serious cavities of the body, originating from the mesoderm.

Enzymatically cleaved intracellularly: usually said of proteins such as proinsulin that are cleaved by enzymes within the cell before being released into the circulation.

Enzyme: a protein, capable of accelerating or producing by catalytic action some change in a substrate for which it is often specific.

Epithelium: the covering of internal and external surfaces of the body, including the lining of vessels and other small cavities.

Equimolar: containing the same number of molecules, or having the same molarity.

Erythrocytes: one of the elements found in peripheral blood; called also red blood cell or corpuscle. Normally, in the human, the mature form is a non-nucleated, yellowish, biconcave disk, adapted, by virtue of its configuration and its hemoglobin content, to transport oxygen.

Escherichia coli: a species of organisms constituting the greater part of the intestinal flora of man and other animals.

ESRF: End stage renal failure.

ETDRS: Early Treatment Diabetic Retinopathy Study.

Etiology: the study or theory of the factors that cause disease and the method of their introduction to the host.

Etiopathogenesis: pertaining to the cause of the development of a morbid condition or of disease.

Etiopathology: see pathogenesis.

Euglycemia: a normal level of glucose in the blood.

Exchange (meal planning): choice between a number of food items.

Exudate: material, such as fluid, cells, or cellular debris, which has escaped from blood vessels and has been deposited in tissues or on tissue surfaces, usually as a result of inflammation. An exudate, in contrast to a transudate, is characterized by a high content of protein, cells, or solid materials derived from cells.

Fascicle: a small bundle or cluster; especially of nerve or muscle fibers.

FBG: fasting blood glucose.

Fetal islet hyperplasia: increase in size of the pancreatic cells secreting insulin in the fetus.

Fibroblasts: a connective tissue cell; a flat elongated cell with cytoplasmic processes at each end, having a flat, oval, vesicular nucleus.

Fludrocortisone: a synthetic adrenal corticoid, with effects similar to those of hydrocortisone and desoxycorticosterone.

Fluphenazine: the 2 trifluoromethyl derivative of perphenazine, the most potent of the phenothiazine tranquillizers.

Fluorescein: the simplest of the fluorane dyes and the parent compound of eosin, used intravenously in tests to assess by its fluorescence the adequacy of the circulation, and combined with radioactive iodine in localization of brain tumours etc.

Formulary: a collection of recipes, formulas and prescriptions.

Ganglioside: a general designation for a member of a class of galactose containing cerebrosides found in the tissues of the central nervous system.

Gap junction: a specific anatomical junction between two contiguous cells.

Gastroenteropathy: any disease of the stomach and intestines.

Gastroparesis: paralysis of the stomach.

Gel filtration: a column technique which separates compounds according to their size.

Genome: the complete set of hereditary factors, as contained in the haploid assortment of chromosomes.

GHEG: Good Health Eating Guide.

Glipizide: an oral hypoglycemic drug of the sulfonylurea group.

GFR: glomerular filtration rate.

G.I. peptide: gastric inhibitory peptide; it is a gastrointestinal hormone.

Glomerular hyperfiltration: increase in glomerular filtration rate.

Glibenclamide: an oral hypoglycemic agent of the sulfonylurea group, used in adult-onset diabetes.

Glomerular: pertaining to, or of, the nature of a glomerulus, especially a renal glomerulus.

Glomerular filtration rate: the rate at which the blood is being filtered through the kidney.

Glomerulosclerosis: lesions of the glomeruli of the kidney.

Glucagon: a polypeptide hormone secreted by the alpha cells of the Islets of Langerhans in response to hypoglycemia or to stimulation by the growth hormone of the anterior pituitary; it stimulate glycogenolysis in the liver, and tends to raise the blood sugar.

Glucometer: a reflectance meter used to measure blood glucose.

Glucose challenge: the ingestion of glucose for the purpose of confirming or eliminating the diagnosis of diabetes, or abnormalities in glucose disposal.

Glucosuria: the presence of glucose in the urine.

Glycosylation: the linking of a molecule of glucose to a protein.

Glycosylated hemoglobin: the linkage of glucose to the hemoglobin; this reflects the blood glucose control over the preceding two to three months.

Haplotypes: the group of alleles of linked genes contributed by either parent; the haploid genetic constitution contributed by either parent.

HbAlc: glycosylated hemoglobin.

High affinity antibody: antibody with a high affinity for the antigen.

HDL: high-density lipoprotein.

HDLC: HDL-cholesterol or high density lipoprotein-cholesterol.

Hepatic: pertaining to the liver.

Hepatic gluconeogenesis: new formation of glucose by the liver from non-glucose precursors.

Hepatocyte: a parenchymal liver cell.

Heterogeneity: the state or quality of being heterogeneous. In genetics, the production of identical or similar phenotypes by different genetic mechanisms.

Heterozygotes: an individual possessing different alleles in regard to a given character.

Histocompatible: capable of being accepted and remaining functional; said of that relationship between the genotypes of donor and host in which a graft generally will not be rejected.

HLA: histocompatibility antigens on the surface of nucleated cells determined by a single major chromosomal locus, the HL-A locus, they are important in cross-matching for transplantation procedures.

Hormonal: pertaining to, of, the nature of a hormone.

Hormone: a chemical substance, produced in the body by an organ or cells of an organ which has a specific regulatory effect on the activity of a certain organ.

Hormone biosynthesis: the synthesis of a hormone within a living cell.

Human biosynthetic proinsulin: the synthesis of human proinsulin by recombinant DNA technique using microorganisms such as the E. coli.

Hyalinosis: hyaline degeneration.

Hydrophilic: readily absorbing moisture.

Hypercholesterolemia: excess of cholesterol in the blood.

Hyperglycemia: abnormally increased content of sugar in the blood.

Hyperinsulinemia: the presence of an excessive amount of insulin in the blood.

Hyperinsulinism: 1. excessive secretion of insulin by the pancreas, resulting in hypoglycemia. 2. insulin shock.

Hyperlipidemia: an excess of lipids in the blood, which may be primary, as in disorders of lipid metabolism, or secondary, as in uncontrolled diabetes mellitus.

Hyperosmolar coma: coma due to increased osmolality of the serum (e.g. very high blood glucose).

Hypertension: persistently high arterial blood pressure. Hypertension may have no known cause or be associated with other primary diseases.

Hypertriglyceridemia: an excess of triglycerides in the blood; most common form of hyperlipidemia found in those with diabetes.

Hypoglycemia: an abnormally diminished content of glucose in the blood, which may lead to tremulousness, cold sweat, piloerection, hypothermia and headache, accompanied by confusion, hallucinations, bizarre behaviour, and ultimately, convulsions and coma.

Hypothalmic satiety centre: the centre at the base of the brain (hypothalamus) that controls the aboltion of the desire to ingest food.

IDDM: insulin dependent diabetes mellitus.

IDL: intermediate density lipoprotein.

IgG insulin antibodies: insulin antibodies of the immunoglobulin G class.

IGT: impaired glucose tolerance.

Imipramine: an anti-depressive drug.

IHD: ischemic heart disease.

Immunofluorescence: a method of determining the location of antigen (or antibody) in tissue by the pattern of fluorescence resulting when the tissue is exposed to the specific antibody (or antigen) labeled with a fluorochrome.

Immunogenicity: capacity of producing an immune response.

Immunohistochemical: pertaining to the chemical basis of immune phenomena of cells.

Immunohistopathology: the study of immune basis of diseased cells.

Immunology: that branch of biomedical science concerned with the response of the organisism to antigenic challenge, the recognition of self from not self, and all the biological, serological and physical chemical respects of immune phenomena.

Implantable biodegradable polymer container: an implantable container, which is susceptible to degradation by biological processes.

Incidence: an expression of the rate at which a certain event occurs, as the number of new cases of a specific disease or event occurring during a certain period.

Infarct: an area of coagulation necrosis in a tissue due to local ischemia resulting from obstruction of circulation to the area, most commonly by a thrombus or embolus.

Injectate: solution for injection.

Insulin antibody complexes: the result of the linkage of insulin to an antibody.

Insulinemic: pertaining to the insulin level in the circulation.

Insulin infusion pump therapy: treatment of diabetes by continuous insulin infusion using an insulin pump.

Insulinopenia: lack of insulin in the circulation.

Insulin polypeptide: pertaining to the charateristic of the insulin molecule being a compound containing many peptides, and therefore, many amino acids

Insulin receptor: a chemical grouping on the surface of a cell with the capability to bind insulin specifically.

Insulin receptor kinase: an enzyme, part of the insulin receptor, which can phosphorylate the receptor.

Insulin resistance: being resistant to insulin; requiring high doses of insulin.

Insulin-transporting globulin: globulin, protein transporting insulin.

Intraperitoneal: within the peritoneal cavity.

Intravenous: within a vein or veins.

Ion Exchange chromatography: column technique used to separate compounds according to their ionic charge.

IRMA: intra retinal microvascular abnormalities.

Ischemia: deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel.

Islets of Langerhans: irregular microscopic structures scattered throughout the pancreas and comprising its endocrine portion. They are composed of three types of cells. the alpha cells, which secrete the hyperglycemic factor glucagon; the beta cells, which are the most abundant and secrete insulin; and the delta cells which secrete gastrin.

Isoform: being of similar form.

JDF: Juvenile Diabetes Foundation.

Jet insulin injection: insulin injection by air pressure.

Ketoacidosis: acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissues and fluids, as in diabetic acidosis.

Ketonuria: ketone bodies in the urine, as in diabetes mellitus.

Ketosis: a condition characterized by an abnormally elevated concentration of ketone bodies in the body tissues and fluids; it is a complication of diabetes mellitus and starvation.

Ketosis-resistant diabetes mellitus: diabetes mellitus resistant to ketone formation as in non-insulin dependent diabetes mellitus.

Kinases: a subclass of the transferases, comprising the enzymes that catalyze the transfer of a high-energy group of a donor, usually adenosine tri phosphate, to some acceptor.

Krypton: an inert gaseous chemical element found in the atmosphere; atomic number, 36; atomic weight, 83.80; symbol, kr.

Lability: the quality of being labile. In psychiatry, emotional instability; a tendency to show alternating states of gaiety and sombreness.

Lactic Acidosis: acidosis due to the accumulation of lactate.

Lactogen: any substance that enhances lactation, the principal one being prolactin.

Large Vessel Disease: atherosclerosis of the large vessels.

L'Association du Diabète du Québec: Quebec Diabetes Association.

LDLC: LDL-cholesterol; low density lipoprotein cholesterol.

Lecithin/Sphingomyelin ration: two phospholids that can be measured in the amniotic fluid; their ratio gives a good assessment of the respiratory system development of the fetus.

Lente (insulin-zinc suspension, USP): slow acting.

Lipase: glycerol-ester hydrolase; any of a group of widely occuring enzymes that catalyze the hydrolysis of ester linkages between the fatty acids and glycerol of the triglycerides and phospholipids. They occur in milk, the pancreas, adipose tissue, the stomach, and other tissues.

Lipoatrophy: focal atrophy of subcutaneous fat at the sites of insulin injections.

Lipogenesis: the formation of fat; the transformation of non-fat food materials into body fat.

Lipolytic enzyme: enzyme catalyzing the splitting up of fat.

Lipoprotein: a combination of a lipid and protein, possessing the general properties (e.g. solubility) of proteins.

Local or Systemic Allergy (IgG. mediated): pertaining to local or generalized allergic reaction induced by antibody of the IgG class.

Liposome: a particle of lipoidal material held emulsified in tissues in the format "invisible fat".

Logistic: the art of calculation, common practical arithmetic.

Lumbo Sacral: pertaining to the loins and sacrum.

Lymphocytotoxic: toxic for the lymphocytes.

Macrophages: any of the large, highly phagocytic cells with a small, oval, sometimes indented nucleus and in conspicuous nucleoli, occuring in the walls of blood vessels (advential cells) and in loose connective tissues. They are components of the reticuloendothelial system and are usually immobile, but when stimulated by inflammation become actively mobile.

Macrosomia: of great bodily size.

Macular: pertaining to the macula retinae which is an irregular yellowish depression of the retina related to vision.

Macular edema: swelling of the macula retinae.

Maculopathy: lesion of the macula retinae.

MCV: motor conduction velocity.

Medijector: a spring-loaded device used for insulin injection.

Mesangial: of or pertaining to the mesangium, the thin membrane which helps to support the capillary loops in a renal glomerulus.

Mesangial matrix: the ground work or the basic material of the mesangium.

Metabolic pathway: a series of enzymatic reactions that convert one biological material to another.

Metacresol: one of the three isomeric forms of cresol, and the most strongly antiseptic of the group.

Metabolite: any substance produced by metabolism or by a metabolic process.

Metformin: an oral hypoglycemic agent of the biguanide group.

Metoclopramide: an anti-emetic drug; a drug against vomiting.

Mg/dl: milligrams per deciliter.

Microalbuminuria: micro-quantities of albumin in the urine.

Microaneurysm: a microscopic aneurysm, a characteristic feature of thrombotic purpura.

Microangiopathy: disease of the small blood vessels.

Microencapsulation: the act of introducing into very small capsule.

Mmol/l: millimoles per litre.

Monoclonal antibodies: antibodies derived from a single cell.

"Monocomponent" insulin: purified insulin giving a single peak on chromatography.

Mononeuropathy: neuropathy of a single nerve.

Monozygotic: pertaining to, or derived from, one egg (zygote), as identical twins.

MRC: Medical Research Council.

MRC. RCPSC: Medical Research Council and Royal College of Physicians and Surgeons of Canada (joint task force report).

Mutagenesis: 1. the production of change. 2. The induction of genetic mutation.

Myocardial infarction: necrosis of the heart muscle; heart attack.

Myo-inositol: a stereo isomer of inositol used as aperipheral vasodilator.

Na - K - ATPase: Sodium - Potassium - adenosinetriphosphatase.

Nasal insulin: insulin to be administered by the nasal route.

NDAB: National Diabetes Advisory Board.

Neovascularization: the formation of new vessels.

NVE: neovascularization.

Nephrectomy: excision of a kidney.

Nephrons: the anatomical and functional unit of the kidney, consisting of the renal corpuscle, the proximal convoluted tubule, the ascending and descending limbs of Henle's loop, the distal convoluted tubule, and the collecting tubule.

Nephropathy: disease of the kidneys.

Nephrology: scientific study of the kidney, its anatomy, physiology, and pathology.

Neural: pertaining to a nerve or to the nerves.

Neutral pH: having a pH which is neither acid nor basic (pH-7).

NIDDM: non-insulin-dependent diabetes.

NIH: (U.S.) National Institutes of Health.

NIRA: New Investigator Research Award.

Normoglycemia: the state of having the level of glucose in the blood within the normal range.

Normoglycemic: pertaining to, characterized by, or conducive to normoglycemia.

Normotensive: characterized by normal tone, tension, or pressure, as by normal blood pressure.

NPH: isophane insulin suspension, USP: intermediate acting insulin.

NPH/lente: NPH or isophane insulin and/or lente or zinc suspension insulin; USP: intermediate acting insulin

NVD: neovascularization on the disc.

Oculometer paresis: weakness of the eye muscle.

Oral hypoglycemic agents: drugs which decrease blood glucose used in the treatment of non-insulin-dependent diabetes.

Orthostatic hypotension: a fall of blood pressure on standing up.

Oxidative phosphorylation: the formation of high energy phosphate bonds by phosphorylation of ADP to ATP, in which electrons are transferred from the substrate to oxygen; it occurs in the mitochondria.

Pancreas: a large, elongated, racemose gland situated transversely behind the stomach, between the spleen and the duodenum. Its right extremity, the head, is the larger, and directed downward; the left extremity, or tail, is transverse, and terminates close to the spleen. The external secretion or juice of the pancreas, which passes into the duodenum through the pancreatic duct, contains a variety of digestive enzymes. An internal secretion, insulin, produced in the beta cells, is concerned with the regulation of carbohydrate metabolism. Glucagen, a glycogenolytic hyperglycemic factor, is produced in the alpha cells. Both the alpha and beta cells form aggregates, known as the Islets of Langerhans, scattered throughout the pancreas.

Pancreatectomy: surgical removal of the pancreas.

Pancreatic polypeptide: a hormone secreted by the pancreas.

Pancreatitis: acute or chronic inflammation of the pancreas, which may be asymptomatic or symptomatic. It is caused most often by alcoholism or biliary tract disease; less commonly it may be associated with hyperlipemia, hyperparathyroidism, abdominal trauma, vasculitis, or uremia.

Parenteral: not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc.

Paresthesias: abnormal sensation.

Pathogenetic: pertaining to pathogenesis.

Pathogenesis: the development of morbid conditions or of disease; more specifically the cellular events and reactions and other pathologic mechanisms occurring in the development of disease.

Pathophysiology: the physiology of disordered function.

PDF: Post Doctoral Fellowship.

Perfusion: the act of pouring over or through, especially the passage of a fluid through the vessels of a specific organ.

(Endothelial) pericytes: one of the peculiar elongated cells with the power of contraction, found wrapped about precapillary arterioles outside the basement membrane.

Perinatology: the study of the events occurring in the period shortly before and after birth.

Pharmacokinetics: the study of the action of a drug in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Ph.D.: Doctor of Philosophy.

pHI: human pancreatic insulin.

Phenformin: an oral hypoglycemic agent of the biguanide group.

Phenol: (USP) an extremely poisonous, colorless to light pink, crystalline compound, obtained by the distillation of coal tar, and converted by the addition of 10 per cent water, into a clear liquid with a peculiar odor and a burning taste. Used as an antimicrobial agent.

Phosphorylation: the process of introducing the trivalent PO group into an organic molecule.

PHWS: Professional Health Worker Section of the Canadian Diabetes Association.

PI: porcine insulin.

Plantar: pertaining to the sole of the foot.

Plasma insulin level: the concentration of insulin in the circulation.

Plexopathy: in reference to the pathology involving a nerve plexus.

Polycycstic: containing or made up of many cysts.

Polyhydramnios: hydramnios.

Polymer: a compound, usually of high molecular weight, formed by the linear combination of simpler repeating molecules, or mononers.

Polymerization: the act or process of forming a compound (polymer), usually of high molecular weight, by the combination of simpler molecules.

Polymorphism: the quality or character of occurring in several different forms.

Polyol pathway: the metabolic pathway leading to the formation of sorbitol.

Polypeptide: a peptide which on hydrolosis yields more than two amino acids; called tripeptides, tetrapeptides, etc., according to the number of amino acids contained.

Polyradiculopathy: disease process involving more than one nerve root.

Polyunsaturated: having many unsaturated bonds and tending to be liquid at room temperature; said of fats and oils.

Polyvinylchloride: a substance formed by the polymerization of vinyl chloride; a tasteless, odorless, clear hard resin, which changes color on exposure to ultraviolet light or heat.

Post-prandial: occurring after dinner, or after a meal.

Precursor: in biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another.

Prevalence: the total number of cases of a disease or event in existence at a certain time in a designated area.

Primary glomerulonephritis: an inflammatory reaction of the glomeruli of the kidney.

Prodomal: premonitory; indicating the onset of a disease or morbial state.

Professional Health Workers Section of the Canadian Diabetes Association: the section of the Canadian Association grouping the paramedical professions interested in diabetes.

Proinsulin: a precursor of insulin, with a weight of 8,000 to 10,000, that has low biologic activity but yields true insulin on tryptic digestion IN VITRO.

Proliferative disease: is said of advanced retinopathy where there is a proliferation of new vessels on the retina.

Prompt insulin-zinc syspension: rapid acting insulin.

Propositus: the original person presenting with, or likely to be subject to, a mental or physical disorder and whose case serves as the stimulus for a hereditary or genetic study.

Protamine zinc insulin: long acting insulin.

Protamine zinc/ultra lente: protamine zinc insulin suspension and zinc insulin suspension, both being long acting insulin.

Proteinuria: the presence of an excess of serum proteins in the urine.

Polydipsia: excessive thirst persisting for long periods of time, as in diabetes mellitus.

Polyuria: the passage of a large volume of urine in a given period, a characteristic of diabetes.

Posterior vitreous fluorophotometry: the measurement of leakage of the retinal vessels into the vitreous fluid by fluorophotometric technique.

Pyridoxine: one of the forms of vitamin B_6.

Radioimmunoassay: determination of antigen or antibody concentration by means of a radioactive-labeled substance that reacts with the substance under test.

Radiculoneuropathy: a neuropathy involving a specific nerve root.

Radionuclide imaging: a quasi-pictorial representation of the distribution of radioactive material in the body.

RCPSC: Royal College of Physicians and Surgeons of Canada.

Reagent: a substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances.

Receptor: a specific chemical grouping on the surface of an immunologically competent cell with the capability of combining specifically with antigen. The lymphocyte surface probably contains receptors closely similar structurally to the antigen-binding of antibody.

Recombinant DNA: a technique using genetic recombination in microorganisms to synthesize specific proteins such as human insulin.

Regular, semilente: regular and semilente insulins are two rapid acting insulins.

Remyelination: restoration of the myelin sheath of a nerve or nerves.

Saturated: unable to hold in solution any more of a given substance.

sHI: semisynthetic human insulin.

Sequelae: plural of sequala: any lesion or affection following or caused by an attack of disease.

Serum creatinine: see creatinine.

Somotostatin: a hormone produced by the hypothalamus and the Islets of Langerhans; among its many aspects it can suppress insulin and glucagon secretion.

Somatostatin analog: an analog of somatostatin.

Sorbinil: an aldose reductase inhibitor.

Sorbitol: a crystalline, hexahydric alcohol, first found in ripe berries of the tree Sorbus aucuparia, and occurring in small quantities in other berries, cherries, plums, pears, etc. It is formed in mammals from glucose, and is then converted to fructose; this process is responsible for fructose found in seminal plasma. It is also found in lens deposits in diabetes mellitus. A pharmaceutical preparation is obtained by catalytic hydrogenation of glucose and certain other sugars; it contains between 91 and 100.6 per cent sorbitol, calculated on the anhydrous basis; used as a flavouring agent. It is also used as an osmotic diuretic.

Sphincter EMG: electromyogram of the sphincter muscle, a band of muscle fibres that constricts a natural orifice.

Starvation ketosis: increased ketone bodies in the blood due to fasting.

Storage granule: cytoplasmic organel used to store hormones before they are released into the circulation.

Streptozotocin: a chemical compound used to induce diabetes in animals; it is also used for the treatment of cancer of the pancreas in man.

Substrate: a substance upon which an enzyme acts.

Sulfated insulin (SI): insulin treated with sulfuric acid to render it less immunogenic.

Sulfhydryl bond: a bond with the univalent radical, - SH.

Sulfonylureas: a group of oral hypoglemic agents.

Sural nerve: the nerve of the leg.

Teratogenesis: the production of physical defects in offspring in utero.

Tertiary Structure: spatial structure of a molecule.

Thrombogenic: producing a clot, curd, or coagulum.

Tibialis: a term designating relationship to the tibia.

Titer: the quantity of a substance required to produce a reaction with a given volume of another substance, or the amount of one substance required to correspond with a given amount of another substance.

Tolbutamide: a compound occurring as a white or almost white, crystalline powder; used as an oral hypoglycemic agent.

Toxemia:

1. a general intoxication sometimes due to the absorption of bacterial products (toxins) formed at a local source of infection.
2. toxemia of pregnancy: a group of pathologic conditions, essentially metabolic disturbances, occurring in pregnant women, and manifested by preeclampsia and fully developed eclampsia.

Transpeptidation: the transfer of an amino-group from one molecule to another.

Tridec: Tri Hospital Diabetes Education Centre, Toronto.

Trimester: a period of three months.

UCT: unchanged conventional treatment.

Uremia: the retention of excessive by-products of product metabolism in the blood, and the toxic condition produced thereby. It is marked by nausea, vomiting, headache, vertigo, dimness of vision, coma or convulsions, and an azotemic odor of the breath. It is due to nephron function inadequate to excrete urea and other products of protein metabolism.

Urine estriol level: level of estriol - a naturally occurring, relatively weak, human estrogen, being a metabolic product of estradiol and estrone found in high concentrations in the urine - in the urine.

Uroflometry: continuous recording of urine flow in milliliters per second, using a cylinder placed on a transducer that weighs the urine entering the cylinder and records it on a time scale.

USP: United States Pharmacopeia.

Vaginitis: inflammation of the vagina.

Vascular: pertaining to blood vessels or indicative of a copious blood supply.

Vasculature: the vascular system of the body or any part of it.

Vasculopathy: disease of the blood vessels.

Vasoactive: exerting an effect upon the caliber of blood vessels.

Vasoregulation: pertaining to the regulation of the contraction and/or dilation of vessels regulating the flow.

Virus: one of a group of minute infectious agents, with certain exceptions not resolved in the light microscope, and characterized by a lack of independent metabolism and by the ability to replicate only within living host cells.

Vitrectomy: extraction of the vitreous fluid of the eye.

VLDL: very low-density lipoproteins.

VLDL-cholesterol: cholesterol of the very low density lipoproteins.

WHO: World Health Organization.

Xenon: a chemically unreactive gaseous element found in the atmosphere; atomic number, 54, atomic weight, 131.30.

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